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SYMPOSIUM ON OBESITY*

A REORIENTATION ON OBESITY

ALFRED W. PENNINGTON, M.D.

WILMINGTON, DELAWARE

DURING the past half-century, investigation of the problem of obesity has followed two distinct lines: that of the intermediary metabolism and that of the energy exchange. It would be natural to expect that the two types should merge and support each other in a unified concept of obesity, for, if a defect in the intermediary metabolism causes ingested food to be diverted to storage as excess fat, the total energy exchange should reflect this abnormality. Actually, however, two schools of thought have arisen and contended through the years, and it has only recently become possible to reconcile them. It is interesting that both types of approach to the problem originated with von Noorden, who first suggested a defect in carbohydrate metabolism and later abandoned this as he focused attention on the energy exchange as a means of explaining the phenomena of obesity.

INTERMEDIARY METABOLISM

Von Noorden[1] first suggested a prediabetic state as a cause of obesity and amplified this as follows: "Obese individuals of this type have already an altered metabolism for sugar, but instead of excreting the sugar in the urine, they transfer it to the fat-producing parts of the body, whose tissues are still well prepared to receive it." It immediately became apparent that, if obesity could arise in this way, the adipose tissues, instead of readily releasing for energy the fat that had been formed from carbohydrate, must hold on to it with unusual tenacity; in 1908 von Bergmann announced the "lipophilia" concept, which attracted many investigators.

Those who sought the answer to the problem of obesity in studies of the intermediary metabolism found a number of clues that led them to the view that some defect of carbohydrate metabolism was involved and that the rate of fat storage exceeded that of its mobilization and destruction. An endocrine influence was also thought to exist, as expressed by Falta[2]: "For fattening is necessary a functionally intact pancreas."

In connection with carbohydrate metabolism Lichtwitz, and then Kugelman, found that the blood lactic acid level of the obese after light muscle exercise was much higher than that in normal persons. Proger and Dennig[3] confirmed these results in experiments that took into account the greater energy expenditure of the obese in performing a given task, and they ruled out all possible causes of the increased lactic acid except "definite chemical disturbances in the muscle."

Studies of the intermediary metabolism of fat were all but impossible until the introduction of isotopes and their use in tagging molecules for physiologic experiments. Details of the metabolism of fat and of carbohydrate as well, previously shrouded in mystery, then became clarified, and old experimental findings yielded to new interpretations. It seems, now, to have become clear that the increase in the blood level of lactic acid observed by Proger and Dennig cannot be due, as they thought, to an inability of the muscle tissues to resynthesize glycogen, for glycogen is not normally resynthesized here.[4] An interpretation more in accord with a modern understanding of carbohydrate metabolism is that the tissues of the obese are more limited than normal in their capacity for oxidizing pyruvic acid — the blood levels of lactic and pyruvic acid both reflect the degree to which the tissues fail to oxidize the pyruvic acid formed in them from the glycolytic phase of carbohydrate breakdown.[5] This interpretation, along with Wertheimer's recent finding that pyruvic acid inhibits the oxidation of fatty acids,[6] suggests that obesity may be caused by a defective capacity of the cells for breaking down carbohydrate beyond the stage of pyruvic acid and that the presence of increased amounts of this substance, by inhibit-

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†Internist, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

ing the utilization of fat, causes fat storage to gain the ascendancy over fat mobilization and destruction. This process, which would result in an increased size of the adipose deposits, would require the presence of a functionally intact pancreas.[7] Thus, the concept of obesity as a defect of intermediary metabolism appears to find some modern support.

Energy Exchange

Von Noorden[8] soon abandoned his earlier theory and became preoccupied with studies of the energy exchange in obesity. In 1907 he made the famous classification of "exogenous" and "endogenous" obesity. The latter was to be distinguished by a diminished energy expenditure dependent upon a "slowing of metabolism." For many years the thyroid gland was suspected as being at fault in common obesity; metabolism tests, calculated from a surface-area formula based on body weight alone, gave abnormally low readings in obesity as well as in hypothyroidism.[9] The hypothyroid as well as the entire hypometabolic concept of obesity was largely abandoned, however, when the introduction of Du Bois' more accurate surface-area formula, based on height as well as weight, gave more normal metabolic readings in uncomplicated obesity. In 1930 Newburgh and Johnston[10] announced that endogenous obesity was a misconception. It seemed reasonable that, if a defect of metabolism could account for obesity, the defect would be reflected in the energy exchange, and, since this appeared to be normal, it was concluded that any explanation of obesity other than that of a primarily disturbed appetite must violate the law of conservation of energy.

It is well known that the basal metabolic rate of the obese is normal by the standard test. This means that obese people oxidize as much food per square meter of skin surface as those of normal weight. The use of the surface area as the measuring rod for metabolism tests has been upheld on the ground that, throughout the animal kingdom, there is a constant mathematical relation between the caloric output and the surface area of the body.[11] It has been found, however, that throughout the animal kingdom an equally close mathematical relation exists between the caloric output and the weight of the body[12] and that the only exceptions to this rule are in people of abnormal build.[13] The metabolic rate in obese human beings, when a weight formula is used, is lower than that in human beings of normal build.[9] Therefore, the basal metabolic rate of the obese is normal when the surface area is used as the criterion and subnormal when the weight is the criterion; this is the only essential difference in the choice of the two methods,[13] which apply with fairly equal universality except in the obese.[13] It has been claimed that the surface-area rule is superior to the weight rule because it causes the metabolic rate of the obese to appear normal,[14] a circumstance that gives it greater universality. It must not be forgotten, however, that the purpose of metabolism tests is to find out if the metabolism is normal. The whole question depends on whether the surface-area rule or the weight rule is the correct one to use, and the decision cannot be made on the basis of which one makes the obese come out normal, for that would indicate an a priori assumption that the obese are actually normal, and the assumption would be used to prove itself.

The current metabolic standards were derived from measurements of a supposedly normal group, which included the obese as well as the lean. One of the supposedly normal group, Mrs. McK., was 4 feet, 11 inches, tall and weighed 204 pounds.[14] The metabolic formula arrived at and adopted as a criterion of normality, therefore, assumes that the obese are metabolically normal. Consequently, they must, by mathematical necessity, come out normal when the formula is used.[15] Justification for the selection of the surface area in metabolic calculations originated in the belief that the surface area of the body caused the rate of metabolism to be what it is,[16] but when it was found that the surface area was not causally related to the metabolism no scientific basis for its use remained.[17, 18] The surface-area formula has been useful, empirically, in the clinical diagnosis of thyroid disease. When applied to obesity, however, it merely compares the metabolism with the average in other obese people and does not show the metabolic status of obesity itself. It seems, therefore, that valuable though the surface-area formula may be in clinical diagnosis, its application must be restricted to determining departures from the average in any weight-and-height group of people, and that it should not be used in scientific investigations of the metabolic status of obesity. The question whether the metabolism of the obese is normal or not, therefore, remains at least an open one.

Dynamic and Static Phases of Obesity

In 1940 Rony[19] observed that many people gain weight over an interval and then maintain constant though excessive weight for long periods or indefinitely. To this observation he applied Cannon's concept of homeostasis, through which the remarkable ability of the human organism to maintain constant weight is negotiated.[20] He described obesity as an alteration in the homeostatic forces that regulate the voluntary intake of food to the energy output. In the weight-gaining stage of obesity, which he called the "dynamic" or "progressive" phase, the homeostatic equilibrium was disturbed, disposing to an energy intake greater than the energy expenditure, but in the static phase the two were again equalized. He observed that

positive caloric balance in the dynamic phase did not necessarily cause that phase:

> Positive caloric balance may be regarded as the cause of fatness when fatness is artificially produced in a normal person by forced excessive feeding or forced rest or both. But obesity ordinarily develops spontaneously; some intrinsic abnormality seems to induce the body to establish positive caloric balance leading to fat accumulation. Positive caloric balance would be, then, a result, rather than a cause of the condition.[19]

Rony suggested that the dynamic phase of obesity would be more likely to reveal abnormalities of metabolism than studies of the static phase. Since it would be impossible to know if a person who had been gaining weight was still in the dynamic phase or had already reached the static phase, he suggested that, for study, the dynamic phase be induced by the application of low-calorie diets. The obese person would then lose weight to a level below that at which his weight had become stabilized, and any abnormal metabolic processes of the dynamic phase would be exposed.

Dynamic Phase

Strang and Evans[21] studied the energy exchange of obese persons before and after they lost weight on low-calorie diets. They reported, "When obese patients are reduced by dietary measures alone, the energy exchange diminishes proportionally much more than the weight or surface area." A lowered metabolism in the dynamic phase of obesity seemed, therefore, striking and obvious. In interpreting their careful and painstaking experiments, however, they assumed, as many did at the time, that adipose tissue is metabolically inert. This led them to the view that the weight of the fatty deposits should not be counted when metabolic calculations are made, and they devised a method of calculating metabolic rates, based on the height and the ideal, rather than the actual, weight. In this way the significance of the decline in metabolism became minimized, for, with the actual weight replaced by a constant figure for any given height, the only variable remaining in the metabolic standard was the height. The formula, therefore, was based on height alone, and it gave abnormally high readings for the metabolism of the obese.[22] More recent investigations indicate that adipose tissue, far from being inert, is metabolically very active.[23, 24] The assumption on which the formula of Strang and Evans was based, therefore, can no longer be held valid. It seems more justifiable to interpret the results of their experiments in a simple and direct manner and to conclude that, in the dynamic phase of obesity induced by low-calorie diets, the basal metabolism is abnormally low.

Reconciliation of energy exchange and intermediary metabolism. The finding of an abnormally low energy exchange in the dynamic phase of obesity appears to demand a correlative disturbance in the intermediary metabolism, for it indicates that the large fat stores are not being mobilized and oxidized rapidly enough to maintain a caloric production equal to that which would normally be expected. The problem of obesity, therefore, appears to resolve itself into that of finding an explanation for the decreased rate of mobilization and destruction of fat. In the rare cases of hypothalamic obesity in human beings it has been suggested that the neural mechanism regulating fat storage may be impaired.[24] In other cases of obesity, it seems reasonable to consider the evidence for a defect in the ability of the tissues to oxidize pyruvic acid[3] and the inhibiting effect of this substance on the oxidation of fatty acids.[4] Under these circumstances, much of the fat that is regularly formed from carbohydrate in the body would accumulate in the adipose deposits; the tissues would suffer a relative deprivation of nutriment, and if the deficit were not supplied by an increased intake of food a decline in metabolic rate must ensue. Under conditions in which the voluntary intake of food was allowed free play, the homeostatic mechanisms that regulate appetite to energy needs would dictate an increased food consumption, and thus the subject of the study would become obese.

Confirmatory studies on animals. Rony's concept of the dynamic and static phases of obesity has been found to apply in the genetic obesity of mice[25] and also in the hypothalamic obesity induced by operation on laboratory animals.[26] In both, after a period of weight gain, it has been noted that the weight curve strikes a plateau. Restriction of food intake then causes weight loss, but the lost weight is quickly regained when food restrictions are removed. Many experimenters were first inclined to consider the weight gain in these animals as due to a primary disorder of appetite. It has been found, however, in genetically obese mice and also, recently, in experimental hypothalamic obesity, that there is a retardation in the rate at which fat is mobilized from the adipose deposits.[27, 28] In the dynamic phase of hypothalamic obesity a decline in metabolic rate occurs if the food intake is not increased[29]; on equal amounts of food, animals operated on gain more weight than those not operated on,[29] and also show an increased rate of conversion of carbohydrate into fat.[30]

As an explanation for the static phase of obesity in laboratory animals it has been suggested that "as fat stores become enormous, even the possibly impaired mechanisms for breaking down fat might be sufficient to supply all the fat that the cells can use and thus gradually impair the urge for new fat formation."[30]

Static Phase

The static phase in the rare cases of hypothalamic obesity in human beings may well be explained by the same process as that suggested for hypothalamic obesity in laboratory animals. In cases of obesity

that arise from a disturbance in the intermediary metabolism of carbohydrate, it may be assumed that the neural and hormonal mechanisms regulating the mobilization of fat continue to operate, though hindered by the forces that inhibit fat oxidation. A lowered rate of mobilization of fat per unit of adipose tissue might then be completely compensated for by the greater total mass of adipose tissue, after the subject had reached a certain degree of obesity. More fat would be mobilized, but the inhibition on its use by the general tissues would cause the blood level of fatty acids to increase. Supporting this concept is the finding that in the majority of cases of obesity the fatty acid blood level is elevated.[31] The increased blood level of fatty acids would induce a more rapid oxidation of fatty acids by the tissues.[6] As a result, the tissues would be more adequately supplied from the adipose deposits, and the homeostatic mechanisms that relate the appetite to energy needs would dictate only the amount of food required to maintain the body weight at a constant, though excessive, level. *Thus, obesity might be considered as a compensatory hypertrophy of the adipose tissues, providing for an increased use of fat by an organism that suffers an impairment in its ability to oxidize carbohydrate.*

Implications in Treatment

Low-calorie diets, although they reduce the weight of the obese may, it seems, merely disturb the balance of forces that exists in the static phase and re-establish the dynamic phase of obesity, in which the forces tending to cause weight gain are reactivated. This would mean that treatment had been directed only toward the outward and most obvious symptom of a profound metabolic disturbance, which would continue to promote excessive fat storage unless counteracted by continued caloric restriction. The tendency of people to regain weight lost through dieting is notable.[32] Brown and Ohlson[33] reported cases in which, after reduction of weight, constant weight was maintained on remarkably low food intakes. It seems that the obese person who is treated by the low-calorie method must remain on a subnutrition diet the rest of his life if he wishes to prevent weight gain. If the formerly obese person, with his subnormal caloric expenditure, ate as everyone else does and still did not regain weight the law of conservation of energy would be violated.

Low-calorie diets, it seems, operate not so much by causing the body to "draw on" its fat reserves as by limiting the formation of new fat by withholding the necessary materials. At the same time, these nutrient materials are being withheld from the tissues that require them for energy. It seems desirable, in the treatment of obesity, to direct efforts toward an increased utilization of fat. If this could be accomplished with sufficient effectiveness, no caloric restriction would be necessary, for a large part of the energy needs would be supplied by the body stores, and the homeostatic mechanisms that relate the appetite to the energy output would dictate an intake of food requisite to make up the remainder. Weight would be lost, but a normal caloric production would be maintained. The final result would be what, to extend Rony's terminology, might be called a "negative dynamic" or "retrogressive" phase of obesity, in which the tendency to gain weight on an unrestricted caloric intake would be reversed. There are indications that such a treatment of obesity is quite possible.

Physiologic Determinants in Weight Reduction

The over-all determinant in weight reduction is the degree to which the caloric expenditure exceeds the intake, but a number of physiologic factors determine both these variable quantities. Since much of the carbohydrate as well as the fat ingested is regularly stored as fat before it is utilized,[34] and since fat cannot be reconverted to carbohydrate in any significant amount,[35] the oxidation of fat for energy plays an important part in the continuing metabolism. The significance of the role of fat has only recently been recognized. It is used readily by the general tissues as fatty acids[36] and as the ketones that are formed in the liver,[37] without the necessity of the simultaneous oxidation of carbohydrate.[38] After the usual overnight fast 60 per cent of the energy needs of the body are met by fat,[35] and after two days of fasting this figure is increased to 90 per cent.[39] It appears that the mechanism by which increased amounts of fat are made available for fuel is by means of the ketosis that develops when carbohydrate is in short supply.[40] The ketosis is followed by mobilization of fatty acids from the adipose deposits.[40] Then, with the blood levels of ketones and fatty acids increased, the tissues oxidize both substances at a faster rate.[6, 39] Ketosis is, essentially, a benign process that spares protein[35, 39]; its effect in stimulating the metabolism[41] offsets, to some extent, the specific decline in metabolism attendant on subnutrition. The low-calorie diets employed by Strang and Evans were ketogenic,[42] and this circumstance, it seems, made possible a somewhat favorable contrast between their use in the obese and the use of nonketogenic diets in the nonobese. Unless low-calorie diets are ketogenic, it seems, they cannot operate by increasing the use of fat by the organism but only by decreasing the formation of new fat.

An increased use of fat by the organism can apparently be induced by two methods, which have special applicability to the obese. Restriction of carbohydrate, productive of ketosis in the lean, would be even more effective in the obese if, as there seems ground for believing, the obese on a highly carbohydrate type of diet form an excess of pyruvic acid, for the removal of this excess would

eliminate the inhibition on the oxidation of fatty acids. The ingestion of fat, on the other hand, which ordinarily causes ketosis by stimulating the pituitary gland to produce a ketogenic principle,[42] has three times as great an effect in the majority of the obese as in the lean.[44] In the obese the blood level of ketones induced by fat feeding reaches about 12 mg. per 100 cc. Although this is higher than the level in the lean, it is less than half the moderate level of ketosis found after two days of fasting[39] and only a thirtieth of the level reached in severe diabetes.[45] Reference to ketosis, it seems, should always indicate the actual level of ketones in the blood; otherwise, the benign and even beneficial levels of ketonemia are confused with those associated with severe illness.

The type of treatment of obesity to which these considerations logically lead is that of a diet in which carbohydrate, alone, is restricted and protein and fat are allowed ad libitum. Such a diet was studied thoroughly at the Russell Sage Institute in 1928, though not with the problem of obesity in mind. Subject V. S. of that study, who was a few pounds overweight, lost his excess weight in the first few weeks of an exclusive diet of lean and fat meat.[46] His basal expenditure rose from 60.96 calories to 66.38 calories per hour during the period of weight loss, indicating an increase of 8.9 per cent.[47] He continued on the diet a full year, with no apparent ill effects. His blood cholesterol level at the end of the year, while he was still on the diet, was 51 mg. lower than it had been at the start.[48] It rose a little after he resumed an ordinary, mixed diet. After losing his excess weight he maintained constant weight the rest of the year, though food was taken in as desired. His total intake ranged from 2000 to 3100 calories a day.[46] He derived, by choice, about 80 per cent of his energy needs from fat and 20 per cent from protein. These proportions are close to those derived by a person from his own tissues during prolonged fasting.[49] The instinctive choice of about 80 per cent of the calories from fat seems to be based on selection by the metabolic processes of the organism. It has been found that when carbohydrate is restricted in the diet, the appetite for fat greatly increases.[50] The organism adapts itself to a greater use of fat for energy when this substance is increased in the diet.[51]

The proportion of 80 per cent of the calories from fat and 20 per cent from protein would be represented by one part of fat to three parts of lean meat, by weight. Carbohydrate, as the glycogen contained in the meat, would be present to the extent of 1 or 2 per cent of the calories. In round figures the amounts of food consumed would be from 6 to 9 ounces of lean meat and 2 to 3 ounces of fat, cooked weight, at each of the three meals of the day. The precise amounts ingested were, of course, regulated entirely by the appetite, and they varied from day to day, paralleling the daily variations in energy needs.

This type of diet has been applied clinically in the treatment of obesity and has worked out very well.[52, 53] In most cases the addition of carbohydrate, not exceeding 60 gm. a day, has been found compatible with effective weight loss. Much more than this, it seems, would be likely to check ketogenesis[33] and thus make weight loss impossible on an ad-libitum intake of protein and fat. Carbohydrate foods used were potato, rice, grapefruit, grapes, banana, melon, blueberries and raspberries in amounts yielding an average of not more than 20 gm. of carbohydrate at each meal. In a few cases even this much carbohydrate prevented weight loss, though an ad-libitum intake of protein and fat, more exclusively, was successful. In rare cases, suspected of being cases of hypothalamic obesity, it has been ineffective.

Adjunctive measures have been restriction of salt, for the purpose of increasing the metabolic rate,[54] and liberal amounts of water, for the same reason.[55] A cup of black coffee or tea has been allowed with each meal. A most helpful adjunct, and one that has appeared to be beneficial in many ways in addition to weight reduction, has been the prescription of a half-hour walk before breakfast each morning. This accentuates the fasting state and throws the metabolism over to an increased use of fat for energy.[35, 56] In addition, it appears to drain the liver and gall bladder[57, 58] and to facilitate greatly the handling of fat by the digestive tract.

A remarkable finding in the use of this type of treatment has been the large total caloric intake, which appears to be compatible with a weight loss of 7 to 12 pounds a month. This is not surprising, however, when it is realized that the obese have large requirements for maintaining a constant, though excessive, weight level, and that with this type of treatment there is an increase in the caloric expenditure, rather than a decrease, as in treatment by caloric restriction.

If this concept of obesity and its treatment is accepted, credit must be given to Dr. Vilhjalmur Stefansson, anthropologist and Arctic explorer, who observed that Eskimos were never obese when following their accustomed diet of lean and fat meat but that obesity appeared among them with great rapidity when concentrated carbohydrate foods were introduced, and to Dr. Blake F. Donaldson, who, for two decades when little was known about the intermediary metabolism, applied this type of treatment in his practice and reported on it in conferences at the New York City Hospital.

Summary

It appears possible to reconcile studies of the intermediary metabolism and of the energy exchange in obesity by the concept that this condition arises from a defective capacity of the tissues for oxidizing

pyruvic acid. Evidence for such a defect is presented, and for the chain of metabolic events that would follow, leading to the obese state. A concept of obesity as a compensatory hypertrophy of the adipose tissues is suggested, and a rational basis given for a treatment in which carbohydrate alone is restricted while protein and fat are allowed in ad-libitum amounts.

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LIPOGENESIS*

SAMUEL GURIN, PH.D.†

PHILADELPHIA

IN the field of lipid synthesis, knowledge is still scanty and rudimentary. Although the conversion of carbohydrate to fat by the living organism has been known to biologists for years, the intervening metabolic steps involved are almost completely unknown. For that matter, little is known about the individual chemical reactions concerned with either the oxidation of fatty acids or their biosynthesis.

It has become apparent that the investigator studying the details of such processes must work with as simple a system as possible and, even more important, must attempt to isolate the individual enzyme systems involved in these complex biochemical syntheses. In recent years, in vitro studies supplemented by isotopic and chromatographic technics have begun to yield results. As an illustration, it is possible to incubate liver slices with C^{14}-labeled glucose and subsequently to isolate C^{14}-labeled fat. Thus, it is possible to demonstrate that fat has been synthesized in spite of the fact that the total quantity of fat has diminished during the incubation. Such a result could not be obtained by simple analytical balance studies.

All the information at hand suggests that only substances capable of being degraded biologically to acetate or 2-carbon fragments are utilized by mammalian tissue for the biosynthesis of fatty acids. For example, it has been demonstrated by a number of investigators that rat liver slices can incorporate some of the carbon atoms of glucose, lactate, pyruvate, acetone, acetaldehyde, acetic acid, butyric, hexanoic, octanoic and isovaleric acids into long-chain fatty acids.

The implication is quite clear that carbohydrate must first undergo glycolysis before its utilization for fatty acid synthesis. That pyruvate and acetate can both give rise to active acetate (probably acetyl coenzyme A) is now reasonably certain.

Whereas liver slices of normal rats can readily convert acetate to fatty acids, this is not true of such slices obtained from alloxan-diabetic rats, depancreatized cats, fasted rats or even rats subsisting on high-protein or high-fat diets. The same results are obtained whether one employs acetate or glucose for these studies. Although the addition of insulin to liver slices of normal animals can stimulate the incorporation of acetate or glucose into fat, no in vitro effect of insulin can be demonstrated with liver slices of diabetic animals. On the other hand, Chaikoff's group[1] has demonstrated that lipogenesis in liver slices of fasted rats can be stimulated by the addition of fairly large amounts of glucose or, more effectively, by glucose in addition to insulin. The in vitro stimulating effect of insulin has incidentally also been observed by Folley and French[2] with lactating rat and rabbit mammary-gland slices.

Liver slices obtained from hypophysectomized and pancreatectomized cats can convert labeled acetate into fat at a normal rate. It appears therefore, that lipogenesis is capable of proceeding in the absence of insulin provided the hypophysis is also removed. The addition of purified insulin to such preparations once again results in an acceleration of this biosynthesis.

The striking difference observed between the depancreatized and both hypophysectomized and depancreatized animals suggested that the pituitary gland directly or indirectly exerted an antagonistic effect on lipogenesis. Purified growth hormone (free of adrenocorticotrophic activity) was therefore administered to several hypophysectomized and depancreatized cats and found once again to produce a marked depression of lipogenesis. Prior injection of cortisone into the normal rat also brings about a depression of hepatic lipogenesis by liver slices. Finally, liver slices obtained from adrenalectomized and pancreatectomized cats also retain their ability to synthesize fat.

These results appear to be consonant with the observations of Welt and Wilhelmi[3] that both growth hormone and ACTH depress the biosynthesis of fatty acids in vivo.

Although it is now well established that lipogenesis is seriously impaired in several types of experimental diabetes, the reverse process — namely, the oxidation of fatty acids — is unimpeded or even accelerated. C^{14}-labeled fatty acids are readily converted by such slices to acetoacetate. Similarly, evidence accumulated over the past decade or more indicates that the fasting state is characterized by an accelerated hepatic oxidation of fatty acids and increased ketogenesis. It is therefore clear that there must be an abundance of active 2-carbon units produced by the liver during the "diabetic" or fasting state. These active 2-carbon fragments may condense with oxalacetate to form citrate and become oxidized to carbon dioxide and water; they may condense with each other to form acetoacetate. In the fasting or "diabetic" state the fragments can be utilized to form cholesterol at a normal rate or even at an accelerated rate. It appears that, in these states, there is a considerable amount of energy available that can be utilized for the

*From the Department of Physiological Chemistry, University of Pennsylvania School of Medicine.

†Professor of physiological chemistry, University of Pennsylvania School of Medicine.

synthesis of cholesterol but not of fatty acids. For these reasons it was postulated that the pathways of synthesis and breakdown might be different.

Another explanation of these results can be offered — namely, that efficient synthesis of fatty acids by liver slices requires energy derived from glycolysis. Chaikoff and his co-workers[1] have obtained impressive evidence that this may be so. If fructose is ingested by alloxan-diabetic rats, hepatic lipogenesis by such liver slices is restored provided the precursor is acetate but not glucose. This is different from the effects of insulin administration to a diabetic animal, which restores its ability to synthesize fatty acids from glucose as well as acetate and lactate. These workers have also demonstrated that diabetic and normal liver slices utilize the same amount of fructose as measured by disappearance and conversion to carbon dioxide. Several facts emerge from these data. Whether the block in the utilization of glucose in the diabetic state is at the hexokinase level or is a question of penetration, it is clear that the glycolytic and oxidative enzymes are essentially intact. Since fructose feeding does not stimulate the conversion of C^{14}-labeled glucose to fatty acids, the fructose effects cannot be ascribed to a stimulation of insulin secretion. It has also been demonstrated that the oxidation of lactate and the decarboxylation of pyruvate are not appreciably impaired in the diabetic state. It seems clear, therefore, that the glycolytic and oxidative enzymes are unimpaired in experimental diabetes.

Further evidence has been obtained by Medes, Thomas and Weinhouse,[4] who report undiminished oxidation of acetate by liver slices of fasted rats. It consequently appears that the activation of acetate is not impaired in the fasting state.

One is left with the conclusion that there is a block in the coupling of active 2-carbon units to form fatty acid, which is overcome by fructose, or that lipogenesis of fat from acetate requires not only an acetate-activating system but also the simultaneous participation of rapid glycolysis. It is a reasonable assumption (although not proved) that a common feature of diabetes and the fasting state is a diminished availability of intracellular substrates for glycolysis.

Fortunately, it will be possible to test the latter hypothesis. It is obvious that only a cell-free preparation capable of synthesizing fat can be employed for this purpose since the phosphorylated intermediates of the glycolytic cycle are incapable of penetrating cell membranes. The preparation of a cell-free homogenate of pigeon liver that is capable of converting acetate to long-chain fatty acid has recently been reported.[5] This has been extended to the preparation of a completely water-soluble extract capable of carrying out the same process. Such extracts prepared from livers of depancreatized pigeons cannot perform this condensation. It will be of interest to see whether the addition of the phosphorylated compounds of the glycolytic cycle can restore active lipogenesis in such extracts.

No matter which theory turns out to be the true one, there is little doubt that the diabetic and fasting states are characterized by a tendency for 2-carbon fragments to accumulate in the liver. These may be derived from the oxidation of fatty acids or from carbohydrate intermediates, as well as many amino acids. If the condensation of the fragments to fatty acids is blocked, it is reasonable to postulate a greater diversion of these 2-carbon fragments to acetoacetate and to carbon dioxide. Such a theory would help explain the ketosis of diabetes and of fasting. Since the direct conversion of acetoacetate as a 4-carbon unit to cholesterol by liver slices has been demonstrated,[6] it is reasonable to believe that the accumulation of 2-carbon fragments coupled with increased formation of acetoacetate must result in the accelerated formation of cholesterol frequently observed in diabetes.

It should be pointed out that cell-free preparations obtained from pigeon liver incorporate acetate primarily into long-chain fatty acids rather than into triglycerides. Folley and his co-workers[2] have reported that the addition of glycerol to lactating rattor sheep mammary-gland slices stimulates, under certain conditions, the incorporation of acetate into fat. They suggest, as one possibility, that the stimulating action of insulin is due to increased formation of glycerol from glucose. I have never been able, however, to obtain a stimulating effect of glycerol with rat liver slices or pigeon liver homogenates and extracts. Undoubtedly, the enzyme systems involved in the biosynthesis of triglycerides and phospholipids will receive considerable attention during the next few years. Kornberg and Pricer,[7] for example, have recently obtained from rat liver a partially purified enzyme preparation that is capable of condensing various long-chain fatty acids with L-B-glycerophosphate to form phosphatides.

Although considerable work has been done with mammary gland, there still remains a great deal to do with extrahepatic tissues. Chaikoff's group[1] have demonstrated that rat kidney slices and diaphragm can convert labeled glucose into fatty acids. Popják and Beeckmans[8] reported the conversion of labeled acetate to fatty acids by rabbit intestinal mucosa and lung. Medes et al.[4] similarly obtained evidence that rat heart, spleen and testis are capable of performing the same conversion. That adipose tissue can synthesize fat in vitro has been demonstrated by Wertheimer,[9] Mirski[10] and Shapiro and Wertheimer.[11] It therefore appears that the ability to synthesize fat is widespread. Whether the same enzymes and metabolic steps are involved in all these different tissues must await further chemical fractionation.

Although the addition of insulin to suitably prepared slices of liver or mammary gland stimulates lipogenesis, no such effect has been obtained with cell-free preparations or water-soluble extracts of liver. Nor will these extracts respond in any way to the addition of growth hormone or hyperglycemic factor. It is difficult to avoid the conclusion that the action of insulin depends on intact cell structure and that its effect upon lipogenesis is an indirect one. This implies that insulin, by supplying suitable intracellular concentrations of substrates, provides enough energy of the right kind or sufficient hydrogen donor to drive these synthetic reactions in the direction of synthesis. Many of the in vitro effects of insulin can perhaps be therefore attributed to its indirect generation of a little extra energy of the kind needed to couple with synthetic reactions.

In the short time available, it has been impossible to do justice to the pioneer work of such investigators as Drury,[12] Stetten et al.,[13-15] Rittenberg and Bloch,[16] Bloch[17, 18] and a host of others. Meanwhile, the biologist is left with the most difficult task of all — the integration of these isolated facts, so that they may be properly evaluated in the light of the behavior of the whole organism, in health and in disease.

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HEALTH AND OBESITY*

DAVID P. BARR, M.D.†

NEW YORK CITY

IN his delightful monograph on obesity, Leonard Williams[1] has occasion to discuss its classification, as follows:

> The unlovely condition called corpulence or obesity has been divided into three stages known respectively as the enviable, the comical, and the pitiful. Such classification is based upon a false estimate of values, for no case of obesity is enviable. Most of them are in a sense comical, and all are pitiable.

It is not difficult to demonstrate that obesity is both disadvantageous and dangerous. A mere list of its hazards, disabilities and discomforts is formidable. Obesity predisposes to diabetes, increases the tendency to hypertension, favors the development of atherosclerosis and contributes to heart failure. It increases the incidence of gallstones. It causes shortness of breath on exertion, intolerance to heat and excessive sweating. It leads to maceration, intertrigo, eczema and furunculosis. It fosters the development of postural emphysema, flat feet, hernia and osteoarthritis of the hips and knees. In every physical activity, its presence constitutes a burden varying only with the degree of adiposity. It is unesthetic, socially unacceptable and psychologically crippling. It shortens a life that has been made ridiculous and miserable by its presence.

To the uninitiated such an indictment might seem prejudiced and exaggerated. Actually, the itemization of disadvantages and hazards does not distort the facts, many of which have been common knowledge for generations whereas others have been validated by more recent statistical, pathological and clinical investigation. At present the evidence is so convincing that obesity may be truly regarded as a stop signal, a red light of warning for the attention of all who desire vigorous health and long life and for the profession whose duty it is to guard the health of others.

Obesity has not always been so considered. It is true that throughout the ages a few perceptive physicians have held to the idea that gluttons have a high morbidity and mortality and that the spare and the frugal enjoy greater average longevity and relative freedom from vascular accidents. Among the laity also the disadvantages of overeating have

*From the Department of Medicine, New York Hospital-Cornell Medical Center.

†Physician-in-chief, New York Hospital; professor of medicine, Cornell University Medical College.

been given lip service. "He is eating himself to death" and "he is digging his grave with his teeth" have been adages in common parlance for generations. In spite of these occasional warnings obesity has in general been regarded as a grim joke. Fat people have been characterized as happy and jolly, and many, like Caesar, have preferred them:

> Let me have men about me who are fat;
> Sleek headed men and such as sleep o'nights;
> Yond Cassius has a lean and hungry look;
> He thinks too much: such men are dangerous.

In general, physicians of the past were slow to recognize the relation of diet to obesity or the dangerous consequences of overweight. It is indicative of this fault in perception that the benefits of dietary treatment were first emphasized and popularized by a layman some years before Helmholtz's laws of the conservation of energy had been applied to the metabolism of the human body and before caloric balances had been considered in dietary treatment. William Banting,[2] finding that his own incapacitating adiposity excited little interest and enlisted no help from many London practitioners whom he had consulted, devised with the help of an anonymous physician a diet that caused most satisfactory reduction in weight. In 1863 he published privately a little book, *A Letter on Corpulence*. Its first sentence is illuminating: "Of all the parasites that affect humanity I do not know of nor can I imagine any more distressing than that of obesity, and having just emerged from a very long probation in this affliction I am desirous of circulating my humble knowledge and experience for the benefit of my fellow man, with an earnest hope that it may lead to the same comfort and happiness I now feel under the extraordinary change — which might almost be termed miraculous had it not been accomplished by the most simple common sense means." The sensible and not too restrictive diet that Banting proposed received wide attention in England and provided a start for the "banting" that still goes on among his countrymen.

Efforts to prove by statistics the relation of overweight to mortality began with a paper by Rogers,[3] presented at a meeting of the Association of Life Insurance Medical Directors in 1901. He was able to show in the aggregate 135 per cent of the expected mortality in a group of approximately 1500 men who were 30 per cent or more overweight. It was twenty-nine years later that Dublin[4] presented a study on the influence of weight on certain causes of death that has been influential in stimulating a vast amount of investigation and evaluation. Recently, scrutiny has been focused to a constantly increasing degree on the relation of overweight to the morbidity and mortality of cardiovascular disease. This is a natural emphasis since in these days of longer life expectancy and generally aging population this group of maladies constitutes the greatest cause of death.

Hypertension

Several extensive reports have been made concerning the relation of obesity to hypertension: by Thompson[5] on the association among Metropolitan Life Insurance Company employees; by Master, Dublin and Marks[6] on a sample among 74,000 industrial workers; and by Levy et al.[7] on 22,741 Army officers. The results have indicated that in every age and in both sexes a steady progression of blood pressure, both systolic and diastolic, occurs with each increase in body weight per height of the patient. Levy and his associates have shown that sustained hypertension develops in the obese at a rate two and a half times as high as that in those of normal weight.

Some doubt has recently been cast upon the value of these statistics because of the difficulty of obtaining accurate blood pressure in people with fat arms. Indeed, it has been shown that in the obese person pressures recorded directly by a needle within an artery are consistently lower than those obtained with sphygmomanometers in ordinary use. Although this discrepancy has undoubtedly introduced a variable error in the statistical investigations, it does not invalidate the claim that corpulence is an important contributing factor in the development of high blood pressure.

Atherosclerosis

There is much evidence that obesity influences the rate of formation of atheromatous patches in the larger arteries. At Bellevue Hospital Wilens,[8] in a study of 1250 consecutive miscellaneous autopsies, found advanced atherosclerosis twice as frequently in obese as in poorly nourished persons. Furthermore, twice as many of the latter had little or no atherosclerosis. Those of medium nutrition occupied a middle position, with less atheroma than the obese and more than the emaciated. The precocity of the process was indicated by the observation that the advanced lesions in the obese of one decade were greater than those of the spare in the succeeding decade. The trend was evident in every subgroup. At ages of twenty-five to fifty-four, 25 per cent of the obese had advanced disease as compared with approximately 7 per cent for those who were poorly nourished. At ages of sixty-five to seventy-four, the rate was 45 per cent for the obese and 20 per cent for the spare. Coronary atherosclerosis of advanced degree showed a relation to overweight that was qualitatively and for the most part quantitatively like that observed in general atherosclerosis.

Diabetes

For many years Joslin has been emphasizing the relation of obesity to diabetes. His statistics in-

dicate that approximately 9 of 10 diabetic patients in whom the disease develops after the age of forty are recruited from the ranks of the corpulent and that actually only 1 in 20 is underweight before the onset.

Nephritis

Chronic nephritis must also be numbered among the serious maladies to which obesity predisposes. For the most part the association is probably secondary and results from vascular changes primarily dependent upon high blood pressure, arteriolar sclerosis, atherosclerosis or the vascular complications of diabetes.

Mortality

Insurance statistics show that, as a group, overweight men and women have a mortality well above the average at every age and that in general the rate is proportional to the degree of overweight.

If no maladies other than hypertension, atherosclerosis, diabetes and nephritis were fostered by obesity, the impact on mortality would be great. As might be expected, the degenerative diseases of the heart, arteries and kidneys contribute most of the extra deaths among overweight persons. The data of Armstrong et al.[9] show the leading position of diabetes, in which the death rate is almost four times higher among the overweight than among the standard insurance risks. Also, the death rate from certain diseases of the liver, biliary tract, and intestines is higher among the obese and, percentagewise, higher than the much more common conditions of nephritis, cerebral hemorrhage and coronary-artery disease. The higher death rate from automobile accidents may reflect the clumsiness of the corpulent. In two categories the mortality of the obese is less than that of the standard risks: the lower suicide rate may reflect the alleged disposition of fat people; and the lower percentage of deaths from tuberculosis is in keeping with the time-honored observation that undernutrition favors the development of that disease.

Benefits of Reduction in Weight

There can be no possible doubt of the undesirability of obesity or of its threat to health and longevity. The question naturally arises whether it is possible to offer hope to people who have been obese for variable and often for long periods. Can they escape in any considerable part the penalties of obesity if they cease to overeat, follow a reduction diet and lose an appropriate amount of weight? These problems are crucial and deserve more than a hasty answer.

No one can fail to be impressed with the almost unanimous testimony from those who have reduced of a regained sense of well-being, tolerance to heat and diminished sweating, as well as greater ease of locomotion. This is by no means all that may be accomplished. Tolerance to glucose, notably reduced in many of the obese who have never shown the clinical signs of diabetes, is usually increased during a period of weight loss.

The high blood pressure that often accompanies obesity is one of the few forms of hypertension that may yield dramatically to treatment. Although the significance of this change may be in some question because of the difficulty of obtaining accurate blood-pressure determinations with the standard cuff on fat arms, there is little doubt regarding the trend or the beneficial effect of weight reduction.

The effect on atherosclerosis in human beings is not known. One of the most encouraging disclosures in experimental animal pathology is the demonstration by Kendall[10] that the atherosclerosis of dogs produced and maintained for several months by administration of thiouracil and a high-cholesterol diet will undergo regression and partial reversal when the offending agents are withdrawn. Of great interest are the suggestive but inconclusive observations of Wilens,[8] who thinks he has shown by pathological studies that a period of emaciation preceding death causes regression of the atherosclerotic process.

Perhaps mention should also be made of Gofman's[11] statement that the SF12 to 100 bodies to which he attributes pathogenic significance in atherosclerosis and that he finds increased in amount in obesity is diminished by a low-fat, low-cholesterol diet.

Some evidence concerning possible benefits of a reduced caloric intake may be derived from recent reports of the Norwegians, Dedichen, Ström and Adelstrom-Jensen,[12] who compared the mortality from circulatory disease in Oslo during the years 1940 to 1945 with that of the periods preceding and following them. These years were chosen because of the rigid restrictions in food intake imposed on the population in wartime. Shortly after the beginning of deprivation there was a definite reduction in mortality, which reached a minimum at about the end of the third year and continued without further considerable change until the restrictions were removed. It then rose again, finally attaining a level observed before the beginning of the deprivation. Still more interesting was the disclosure that the incidence of thromboembolic phenomena after surgical operations displayed an almost identical curve. This study seemed to indicate that reduction in the previously abundant high-fat, high-calorie diet of the peacetime Norwegians could have had a beneficial influence not only on the mortality from circulatory disease but also in preventing intraluminal clotting.

Prevention and Correction

If, as it now appears, the prognosis of the corpulent may be improved by reduction in weight,

great efforts should be made to accomplish this decrease. Numerous people are fatter than they should be. Armstrong and his co-workers[9] have estimated that in this country alone there may be 15,000,000 who are at least 10 per cent over-weight and that there are more than 5,000,000 whose weight is 20 per cent above the ideal for their heights and frames. The correction of this situation represents a task of magnitude in which every physician may participate and in which the resources of public-education and public-health agencies may be profitably expended.

Theoretically, the correction of obesity should be easy. Obesity is invariably caused by eating more than is necessary; it may be obviated by eating less.

In the recent studies of the Metropolitan Life Insurance Company it appears that the expectation of life is increased and that the danger of circulatory disease is diminished by reduction in diet. This investigation is based on a review of the mortality rates of people previously refused insurance because of overweight who had reduced their weight satisfactorily before a second insurance examination. Directions for reduction are so simple that they can be presented by the physician and can be assimilated by an intelligent patient in a few minutes. On the other hand, the practical difficulties of carrying out a consistent and long-continued program of reduction are enormous. A few may be mentioned briefly.

There is a widespread impression among mothers, encouraged no doubt by many physicians, that to be big is to be strong and healthy. As a consequence, growing children are supplied not only a sufficient amount but actually an excess of food. Habits of overeating are acquired, and admiration for prowess at the table is instilled. There is still current the belief that overweight offers insurance against the development of tuberculosis. More important is the fact that there are vast numbers of people who are dissatisfied, restless and anxious and who substitute overeating for occupation, for love and for unfulfilled sexual desires. Above all, the chief bane of preventive medicine applies to the obviation of obesity as it does to many other admirable corrective measures. This major impediment is the belief, "It can't happen to me," the psychologic attitude that permits excessive smoking of cigarettes by those who know that such a practice may predispose to cancer of the lung and to serious peripheral vascular disease, that permits excessive drinking of alcohol in spite of the realization of its deteriorating effects and that allows the assumption of extraordinary hazards in driving an automobile or in jaywalking on a crowded avenue by those who are well acquainted with the danger. Many a fat physician, thoroughly persuaded of the disadvantages and dangers of corpulence, will continue to overeat, in the conviction or impression that accidents may happen to others but are unlikely to affect him. These are some of the real difficulties that interfere with the application of a simple measure of preventive medicine. They should not deter the thoughtful physician in his constant efforts to prevent overweight in his patients — and in himself.

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RELATION OF OBESITY TO LONGEVITY

LOUIS I. DUBLIN, PH.D.*

NEW YORK CITY

THIS symposium, devoted to the subject of obesity, is a good indication of the growing awareness of the medical and public-health professions of the importance of obesity in the national health picture. Over the years vast changes have taken place in the daily life of people, and the eating habits that were formerly suitable for farmers, factory workers and housewives who had to do a great deal of manual labor are no longer suitable in the highly mechanized America of 1952. The pleasures of eating, however, are just as real today as they ever were, and there is no lack of food. Consequently, although there has been a radical change both in the content of ordinary diets and in the per capita consumption of food stuffs, it is still so easy to put on excess weight that about 1 out of 5 of the nation's adults weigh more than they should. About 5,000,000 of them can by any reasonable standard be classified as obese — that is, 20 per cent above the ideal weight for their skeletal build.

The seriousness of this situation is aggravated by the fact that the conquest of the infectious diseases, as well as major medical and public-health advances along other lines, has enabled a higher proportion of persons to survive to middle and later life than ever before. Under the mortality conditions prevailing fifty years ago, only 62 per cent of the babies born would be expected to survive until the age of forty-five. Today, this figure has risen to 90 per cent. It is all the more important, therefore, that every effort be made to make the middle and later years more healthful for the ever-increasing proportion who are reaching that period of life.

It has been clearly demonstrated time and again by life-insurance and clinical studies that obesity is one of the chief threats to continued good health and longevity in middle and later years. Most convincing have been the series of studies of life-insurance data, which have shown without exception that overweight men and women have a higher mortality than average and underweight persons, and that the greater the degree of overweight, the greater the curtailment of longevity. In fact, especially in men in later life, the best longevity record was recorded for those who were greatly underweight. There may have been an impression in some quarters that with the recent advances in medicine the penalties of overweight might no longer be serious, and a new study of overweight persons was carried out to determine what recent data would show. It was found that although there had been some improvement in mortality of overweight persons, their position in relation to persons of lighter weight had actually deteriorated. This is largely because the diseases, particularly pneumonia and tuberculosis, that exacted a higher death toll among persons of lighter weight than among those who were overweight, are greatly reduced even among underweight persons. In contrast, the chronic diseases of the cardiovascular system, diabetes, cancer and diseases of the biliary tract now loom larger in the mortality picture, and for all these the mortality is definitely higher among overweight persons.

In my judgment the best evidence that has been produced to date of the desirability of weight reduction arises out of a subsidiary study made in connection with the recent analysis of the mortality experience of persons who were accepted for life insurance by the Metropolitan Life Insurance Company but who were limited to substandard insurance — that is, charged an extra premium — solely because they were too fat to be taken at standard rates. As noted above, the general experience confirmed the earlier findings that the mortality of these persons is in excess of that of standard risks regardless of age, sex or length of observation. Among this group were a sizable number who on subsequent application for insurance had reduced their weight sufficiently and for a long enough period to justify insurance either at standard rates or at a lower rate than they had originally been charged. A test of this kind is about as objective as one could ask. The volume of material is quite considerable, particularly for the men. The results are based on approximately 2300 people. There were over 1300 men and nearly 400 women in the lowest extra-premium group who were within the weight limits for standard insurance at their subsequent re-examination, and there were about 400 men and 200 women in the higher extra-premium group who subsequently received a reduced rating or, in some cases, standard insurance after weight reduction. The number of deaths totaled 129 among the men and 18 among the women in the first and 36 and 15, respectively, in the second group.

The findings are, I believe, very significant. Among the men in the lower substandard group who reduced, the number of deaths recorded was 113 per cent of the expected as compared with a ratio of 142 per cent of the expected in the entire experience from which they were originally drawn. Among women, the ratio for those who reduced their weight was 90 per cent as compared with 142 per cent in the entire group. For men in the higher substandard group who brought their weight down,

*Second vice-president and statistician, Metropolitan Life Insurance Company.

the mortality ratio was only 109 per cent as compared with 179 per cent in the entire experience from which this group was drawn. Among the women, the ratios were 135 per cent and 161 per cent, respectively. Thus, there was a substantial lowering of mortality among those who reduced — by approximately a fifth for the men and a third for the women in the lower substandard group. The figures when broken down according to age at issue and duration of observation show irregularities that are primarily due to the small size of the samples in some of the subdivisions. The improvement was greatest at the higher ages among men in the most numerous group — those with the smallest rating originally.

Lest there be any misunderstanding of the import of these results, it is desirable to review briefly the way in which the figures were derived. First of all, the data on the rerated cases were based on the period from the date of rerating and not from the date of the original application. Secondly, in the measurement of the results of both the original group and the rerated cases the contemporaneous mortality experience by age and by duration of insurance among standard risks was used. The selection of applicants for insurance, both medically and otherwise, is reflected in exceptionally low mortality during the early years of insurance; thus, the mortality experience among persons thirty-five years of age who have had their insurance only one year is much less than that of persons of the same age who have been insured for five years or more. The mortality yardstick used in this as well as similar studies based on life-insurance risks takes this factor of low mortality in the early years after issue into account. The effect of selection of insurance risks wears off after a time. It is greatest in the first year after the insurance is issued and becomes of decreasing importance with each succeeding year. The effect after five years is relatively little. The fact that these applicants were virtually all subject to medical examination on rerating does not affect the validity of the results because the mortality yardstick used takes the factor of medical examination into account. In brief, the experience on these rerated cases is evaluated by the same rigid mortality standards as the original group to allow for their select status.

The results are measured in terms of the ratio of the observed number of deaths to the number that would have occurred if the group studied had experienced the mortality prevailing among persons insured under standard policies, due account being taken of the age and duration after entry into the experience. Separate tables were used for men and women, and proper allowance is consequently made for sex differentials in mortality in the evaluation of the results.

I may note that the only effect that could not be taken into account was the downward secular trend of mortality, which has occurred among insured persons as well as in the general population. This factor, however, is of little importance in this instance because it involves only the relatively short period between the original date of insurance and the date of rerating.

A review of the causes of death among the insured who received lower ratings after weight reduction, indicates that the major causes of disease show roughly the same amount of decline as was recorded in total results. This conclusion is based upon a comparison of the proportions of deaths from the principal causes among the rerated cases and in the total experience among the overweight persons in the study. In judging the results, one should keep in mind that the average age of the rerated applicants was somewhat higher than that of the original group. Among the men who received lower ratings after weight reduction, slightly over half of all the deaths were due to chronic diseases of the cardiovascular system and kidneys, and this percentage was likewise observed in the total overweight experience. Since the total mortality is reduced by about a fifth in the rerated group, this finding means that the reduction in the mortality from these diseases was of approximately the same order. Cancer and leukemia accounted for about 10 per cent of the deaths among the overweight men who reduced and 11 per cent in the general overweight experience, and diabetes for 7 per cent and 6 per cent respectively. Deaths from other causes among men in the rerated group were too few to yield reliable comparisons. Among women, the total number of deaths involved was too small to warrant analysis by cause.

Although from the point of view of its nature and volume I consider this mortality experience the best evidence so far presented that weight reduction is worth while, other bits of evidence from clinical and statistical studies bear on the point. Ley[1] analyzed the blood-pressure findings at the beginning and end of a five-year period among nearly 3000 overweight persons in relation to the changes in weight that occurred during the period. In judging the results one should realize that some increase in average blood pressures will be recorded normally over a five-year period. Ley found that among those who reduced their weight by 5 per cent or more during the five years there was a decline in the averages of both the systolic and the diastolic pressure whereas in other cases there was an increase in both averages. Furthermore, there was good correspondence between the rate of change in the weight and in the blood-pressure averages, the largest declines in the averages being recorded among those who lost most weight and the largest increases being recorded among those who gained most.

Even after the development of various disorders in obese persons, the prognosis is often improved

if the patient's weight is brought down. A small clinical experience reported by Adlersberg and his associates[3] on 15 overweight patients with hypertension showed generally that those who succeeded in maintaining a lower weight three years or more after a weight-reduction course experienced a reduction in both systolic and diastolic blood-pressure levels. There was fair correspondence between the degree of reduction in weight and blood-pressure readings. Similar studies have been made on obese patients with diabetes. Newburgh[3] demonstrated that among such middle-aged persons with the disease whose weight was brought down to normal levels the response to the glucose tolerance test was normal in three fourths of the cases and was improved in another 10 per cent. Osserman and Dolger[4] also showed that there was an improvement in glucose tolerance among obese patients with diabetes who lost weight and that the degree of improvement was correlated roughly with the degree of weight change. Furthermore, insulin requirements were affected.

In a group of overweight employees of the Metropolitan Life Insurance Company who took advantage of a weight-reduction course some years ago there were 33 with definite physical signs of disease associated with their overweight, chiefly hypertension and heart disease. In a follow-up study of these cases, Fellows[5] found that 17 had suffered no progression of their condition and were better symptomatically and clinically five years after weight reduction than before. All but 2 of these had maintained a considerably lower weight.

These are, perhaps, the best studies from clinical sources in a literature on the subject that is altogether too meager. Nevertheless, with the general body of information available on the excessive frequency and early development of degenerative and metabolic diseases in overweights as compared with persons of lighter weight, as well as the observations of clinicians generally on the benefits accruing to obese patients both before and after the development of these diseases and impairments, there should be little doubt that weight reduction is both desirable and beneficial for the obese person.

There is another important set of facts that bears on the whole subject. Recently, a comparison of vital statistics of a number of countries[6] showed clearly that among younger people the death rates in this country are about the lowest to be found anywhere in the world. However, despite great wealth and splendid medical and public-health resources, this is not true in middle and later life, especially among men. Whereas, admittedly, international comparisons of rates from specific causes of death are fraught with difficulty, there is some indication that the relatively poor longevity record of Americans in middle and later life is due to the high level of mortality from degenerative diseases of the cardiovascular system and to diabetes and other metabolic diseases. There is no doubt in my mind that one of the significant factors in the situation is excessive food consumption. Americans enjoy an abundance of foods in great variety, and despite high prices, the income level of the vast majority of families is high enough to permit them to obtain more food than they require. At the same time, the great increase in the availability and use of labor-saving machinery and devices in the factory, on the farm and in the home has greatly reduced the food requirements of the people as measured in calories. In addition, the recreational habits of too many people tend to be of sedentary types, such as automobile riding, motion pictures, radio and television. Although it is probably true that the change in dietary habits over the years has produced some decline in the average caloric consumption, it has apparently not been great enough.

From the point of view of preventive medicine and public health, overweight, because of the large number of people affected, is the leading health problem among the middle-aged and older people in this country today. At the same time, it is perhaps the one most amenable to correction. Certainly, the means to correction through weight reduction is a simple and practical approach to the control of the degenerative diseases and to certain other conditions, the mortality of which is definitely high in overweight persons. Every effort, therefore, should be exerted to bring home the dangers of overweight to the people and to get them to take positive action to control their weight. This objective needs the active interest and support of many types of health workers, who will do a more effective job if they work together. However, the prime responsibility for weight reduction rests with the obese person himself. Any program for weight control that does not operate on that premise is likely to fail.

It is desirable that propaganda for weight control continue to emphasize the role of the physician because he can be of direct help to the obese patient in many ways in bringing down the patient's weight. At the same time, it must be recognized that this is something of a counsel of perfection because relatively few people who respond to this propaganda will seek medical guidance, however much they are urged to do so. Most will try to reduce on their own, and it is necessary to do what one can to protect them from weight-reducing fads and frauds.

In the broader attack on this problem of overweight, the active participation of public-health departments is vital. They have the resources to do what needs to be done in popular health education, in spreading the gospel of the dangers of overweight, in setting up practical demonstrations of

weight control, in organizing classes or groups for dietary instruction and in providing suitable educational materials that doctors, health workers and the general public can use.

The campaign for weight control must be planned on a continuing basis because for many people the battle against obesity is a life-long affair. The stakes are high, and the rewards for success commensurate, as shown by the results of the new study on the overweight persons who reduced.

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THE PSYCHOLOGY OF OVEREATING

HENRY W. BROSIN, M.D.*

PITTSBURGH, PENNSYLVANIA

THE other participants in this symposium have emphasized the fact that the psychologic factors are crucial in most cases of obesity, including those with severe eating disturbances. The study of these patients with severe maladaptation has provided valuable working insights into the nature of the internal conflicts, and these are of immense aid in more effective management of milder disorders.

As intensive medical experience provides more evidence that most obese patients suffer from emotional conflicts that can be described and altered, physicians will be able to treat them with greater confidence and success. The newer studies by psychoanalysts of the conflicts leading to overeating and the reciprocal relations between overeating and anorexia in the same patient sharpen clinical observation and broaden the conception of the meaning of food intake as a means of adaptation in both health and disease. That food intake has psychologic as well as caloric significance is no news, but the purpose served by various patterns of eating is only now being worked out with sufficient detail in a sufficient number of cases to make a convincing demonstration and to provide better leads to effective therapy.

Time does not permit the presentation of evidence from patients that they are aware of the relation between their eating patterns and their emotions, but attention is called to the demonstration by Freed[1] that 93 per cent of 500 obese patients were aware of such connections. Incidentally, the dynamics of obesity are found in many different psychiatric diagnostic types. Accurate diagnosis is essential because not all overeating need be regarded as pathologic. Some grossly overweight patients may be suffering from a severe depressive state even though most depressive patients eat poorly. A few such patients may oscillate between states of obesity and anorexia.

*Professor of psychiatry and chairman, Department of Psychiatry, University of Pittsburgh School of Medicine; director, Western Psychiatric Institute and Clinics.

The demonstration of this reciprocal relation in a therapeutic setting, where the activities of the therapists influence directly the fluctuations in weight, is an impressive clinical experiment. The study reported by Szurek and his co-workers[2] (after twenty months of observation) may be cited as an example. The patient, a twelve and a half-year-old girl, was admitted to the hospital with a presenting complaint of a weight loss from 98 pounds to 53 pounds because of a severe self-imposed starvation. She had been a pretty, somewhat obese girl before the present illness. Friends at school suggested that she diet because she was fat and unattractive; a friendly boy turned his attention to another neighborhood girl; her father was severely beaten by this girl's relatives in a quarrel. This last event became of greater importance because it signaled the loss of status in the parents' own eyes and in those of the patient. Weight loss was precipitate after this, and her cadaverous appearance finally compelled action. In view of the poor prognosis and the poor treatment progress reported by others, the authors decided to attempt more active therapeutic measures by having one therapist with the mother and another with the father while a third treated the child. All were supervised by Dr. Szurek. The manifold tribulations of this team are described briefly but with sufficient content to enable the reader to gain some knowledge of the methods of collaborative therapy in a severely ill patient. The importance of skillful interpretation and supervision of the unconscious processes of both the patient and the inexperienced therapist by means of thoroughly honest and frank reviews is well demonstrated. The cost in time, energy and enduring patience presents a picture that will correct an uninformed optimism. The positive demonstration that psychologic methods can alter the cachectic state to one of obesity in the same patient favors the hypothesis that these syndromes are related dynamically. Time does not permit a review of the extensive literature that followed

Freud and Abraham, who described the basic conflicts, but a few outstanding relations, though tentative because the case is not yet completed, can be described.

It is readily recognized that in some families food is an important means of obtaining both real and symbolic satisfactions for deficient rewards from other interpersonal transactions. Parents who have suffered starvation and other deprivations may use food to build up their own importance to their children and to reassure them against racial and economic insecurity. On the other hand, if the child refuses to eat, the interpretation may be made that she is publicly exhibiting the failure of the parents to give the child the sustenance ("supplies") it needs. Such self-imposed starvation is representative of strong hostility to the parents that may end in suicide. In the overeating phase, however, the girl may be using food as an additional substitute for the thin rations of affection that the parents can offer. Within limits the girl can keep her equilibrium by greater dependence upon food, but if there is a radical change in even her usual poor intake of "supplies" she will suffer a major personality reorganization, which may be that of a severe psychosis.

The therapeutic progress of the patient referred to above may be described as a process in which the girl's hostility to herself and to her parents was deflected upon her therapist. Simultaneously, she obtained from him and other ward personnel some gratifications (intake, supplies) that made the self-directed hostility less essential and thus enabled her to eat. As the parents regained confidence and self-respect from their therapy, they were able to give her more "intake" and thus encouraged her to eat. The authors point out that the mother through her overeating and depressive tendencies, the father through his alcoholism and the patient through her return to an obese state have not really solved their basic problems. The reversal of an obese state to a cachectic one and a return to the obese is, however, of independent importance.

Some attempts at grouping the various emotional conflicts involved can be appraised. Reeve[3] described two groups, the first of which centered around the satisfactions gained principally from the symbolic value of the obese state. Other writers have also furnished support for the concepts that the enlarged body may represent a fortress-like defense against a hostile world, a symbol of independence, importance and prowess, an intimidation to enemies, a symbol for a wished-for pregnancy, a means of discouraging suitors, a mask for emotions or a socially acceptable justification for underactivity that permits the person to take fewer risks and thus helps keep anxiety low. Reeve's second group contains immediate satisfactions gained in the act of eating. It is a question to what extent external interpersonal transactions are associated with this series of operations. Many persons who use food as a means of allaying disquieting feelings can alter their eating patterns effectively when circumstances give them nonfood "supplies" from other sources. This helps explain why obesity may be a self-limiting disorder or why it is amenable to ordinary manipulative therapies, including social clubs modeled upon Alcoholics Anonymous.[4]

It is not generally recognized that reducing regimens are often accompanied by anxiety, depressive or other reactive states, sometimes with suicidal attempts. Dr. Hilda Bruch, one of the ablest investigators in this field, cites a quotation that she says expresses the essence of the obesity problem: "Imprisoned in every fat man a thin one is wildly signalling to be let out."[5] Doctors are well advised to work sensitively and at length with patients in middle life who are overweight. If a hard-working man is deprived of smoking, food or alcohol when he receives little genuine satisfaction from his job or family, one has the obligation to replace them with something constructive. It is possible to see a kind of equivalence between one set of activities and another. A patient may defend himself from a depressive, irritable state by reading, television, motion pictures (visual intake) or other outlets such as sports, fast motor cars, hunting, sailing and gambling. If appropriate equivalent activities are not available, the patient and his entire family and business associates are put under stress. To obtain good results one must study the total picture and treat the patient accordingly.

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MEDICAL PROGRESS

TREATMENT OF PEPTIC ULCER

Louis Zetzel, M.D.*

BOSTON

THE recent publication of two voluminous books[1, 2] on peptic ulcer as well as the profuse literature[3] on this subject attest to the importance of a disease that has an annual mortality of 10,000[4] in this country and affects 5 to 10 per cent of the adult male population in the United States and England.[5, 6] The present report is a brief review of current opinions regarding the medical treatment of peptic ulcer and its complications. The relative merits of various types of surgical treatment, such as gastric resection and vagotomy, are not discussed.

Progress in the treatment of any condition is usually the result of an increase in knowledge of its etiology and pathogenesis. Any treatment of peptic ulcer that does not rest on this sound basis makes its appeal to physicians and patients alike on the alluring promise of short cuts to health. Treatment to be effective should be adapted to what is known about the disturbed physiology of the gastrointestinal tract, its associated features and pathological sequelae.[7]

General Considerations

Peptic ulcer is a chronic disease involving the upper gastrointestinal tract in areas exposed to an acid gastric juice. Acute erosions may occur in the absence of hydrochloric acid but heal without going on to the formation of a chronic peptic ulcer. The ulcer, with few unpredictable exceptions, retains its tendency to recurrence of activity, in spite of any treatment now available. In this sense the disease is incurable. Even radical surgery, unless it results in a permanent achlorhydria, may not always afford protection against recurrence. Therefore, any claim that a projected form of treatment can do more than relieve acute symptoms is to be viewed with skepticism. The effectiveness of any treatment should be judged not only by its ability to afford prompt symptomatic relief but also by its favorable influence on the healing of the ulcer and prevention of recurrences and complications. The frequency of apparently spontaneous remissions without any obvious change in the patient's regimen makes it necessary to institute proper control studies to eliminate the weighting effect of the physician's enthusiasm and the patient's hope for any new treatment, before its specific therapeutic role is assessed. In the past, new fashions in treatment, drugs and diets have come and gone, heralded by extravagant claims, supported only by the uncritical testimonials of patients, soon to be followed by disappointments and waning of interest as the supposed cure grew stale with the passage of time. Fortunately for the patient who heeds the warning signal of hunger pain by instinctively eating under these circumstances, the symptoms of activity are often brought under control without any of these panaceas.

Principles of Treatment

Although Cruveilhier,[8] nearly a hundred years ago, discussed some of the principles of medical treatment as they are known today and Fenwick,[9] in 1868, stressed the importance of small, bland feedings and sodium bicarbonate to control gastric acidity, it was Sippy[10] who, in 1915, emphasized the strict, progressive bland diet with massive alkalinization to protect the ulcer from the corroding effect of gastric juice. This treatment, which remains the basis of modern medical management of peptic ulcer,[11] operates on the assumption that one is dealing with the interaction of two forces: mucosal resistance and the influence of acid gastric juice. This in no way restricts the therapeutic horizon to the area of the observed lesion but must include consideration of the patient himself, as well as his internal and external environment and their influence on his secretion of acid juice and its effect on gastric, duodenal or esophageal mucosa.

"No acid, no ulcer"[12] remains a valid truism, the keystone of current medical practice:

> No dispute about the etiological significance of acid can minimize the importance of its role in ulcer treatment. Both medical and surgical therapy are founded on the premise that reduction and abolition of acid will lead to the relief of pain and healing of the ulcer.[13]

Although there have been several recent reports of peptic ulcer with achlorhydria,[14-17] the overwhelming weight of evidence establishes the presence of free hydrochloric acid as the *sine qua non* of ulcer activity.[18] Certainly, relief is associated with measures that diminish the amount of acid in the stomach.[19] The natural tendency of the ulcer to heal even without the benefit of medical care in uncomplicated cases and the frequent recurrence of activity in spite of medical supervision during the previous attack have led to an attitude of therapeutic nihilism on the part of physician and patient alike. Many patients find it difficult to believe it essential to continue on their restrictive regimens when they have previously remained asymptomatic

*Clinical associate in medicine, Harvard Medical School; associate visiting physician, Beth Israel Hospital.

for months in spite of varying degrees of neglect. They misinterpret these temporary remissions of symptoms as the absence of all potential disease.[20] No present measure can alter the patient's basic tendency to suffer recurrences. Nevertheless, maintenance of a suitable regimen may prolong his remissions and lessen the severity of the complications or even hold them in abeyance.[21] To this end the physician must guide his patient and help him institute a medical program that is simple and practical so that it will enlist his co-operation rather than prescribe a diet that resembles a "penitential fast"[22] and hand out a printed routine so uncompromising and exacting as to evoke only resentment and noncompliance.[23] The patient in turn must recognize that his condition is part of a continuing problem that may be controlled rather than cured.[24]

Over-All Results of Treatment

The status of medical treatment is satisfactory for the acute, uncomplicated attack. The results are much less gratifying when judged by the small proportion (3 to 10 per cent) of patients who remain symptom free without recurrence of activity for two years.[25-30] Conservative medical treatment is still the first choice, though one of the major deterrents to radical surgery in the past is gradually being removed by a decrease in its hazards and by improvement in its long-term results.[31] Of 444 patients followed for five years at the Hospital of the University of Pennsylvania, 36 per cent required operation, and an additional 11 per cent were considered medical failures.[32] Of the patients subjected to operation, the results were satisfactory in approximately 80 per cent as opposed to a satisfactory result in only 50 per cent on a medical regimen. "While surgery should be out of sight in the wings awaiting its cue to come on, the difficulty lies in determining when in the absence of danger signals the orange light that precedes the red light has begun to show."[21] Moore et al.[33] recently evaluated the clinical course of 997 patients, 738 of whom were treated by nonsurgical measures. On the basis of this study, prognostic criteria were classified in two groups. Under primary criteria the following were listed: one perforation with persistence of symptoms; one acute hemorrhage requiring transfusion; and progressive pain over a two-year period while the patient is under a physician's care. The secondary criteria included: a male patient with duodenal ulcer and symptoms under a physician's care; and a male patient with the onset of symptoms before twenty or after sixty-five years of age. In any patient in whom two of these criteria are present, one of which must be in the primary classification, the prognosis for a satisfactory result under medical management is poor since, according to this definition, they have a "progressive or virulent ulcer." Under medical management the results were poor in 33 per cent, only fair in 22 per cent and good or excellent in 45 per cent. In contrast, of 155 patients treated by subtotal gastrectomy, the results were poor in 12.3 per cent, fair in 11.6 per cent and good or excellent in 76 per cent. The definition of poor results after operation, included patients who died or were unimproved or in whom the "dumping syndrome" developed. The results were excellent if the patient remained asymptomatic without following any ulcer regimen, and in fact was no longer considered a patient. The results were deemed good if the patient was asymptomatic but had to continue some form of medical treatment. All these patients were followed for two to eight years so that adequate time had elapsed after operation to render the results obtained significant. The over-all mortality was 2.8 per cent, with practically no difference in this respect between medical and surgical patients.

Drug Therapy

The acute episode of ulcer activity in most cases subsides spontaneously. However, the duration of the symptoms may be lessened and healing hastened by measures that neutralize or inhibit the production of free hydrochloric acid in the stomach. Complete neutralization is seldom necessary and may even be undesirable.[34, 35] Peptic activity and proteolytic digestion is inhibited at a pH of 3.5 to 4.5, an endpoint that is adequate as the goal in neutralization. This approach to the acid effect on the stomach remains the chief therapeutic weapon.[36]

The ideal drug in ulcer therapy should have the following characteristics: a prolonged neutralizing effect without a secondary or rebound increase in secretion; palatability; capacity to promote healing and prevent or delay the onset of recurrences and complications; effectiveness when taken by mouth; promptness in relief of symptoms; and noninterference with the process of absorption.[37, 38]

Enthusiastic sponsors have made many claims for a succession of drugs introduced on the basis of animal experiments alone, without regard for species differences. Some experiments failed to take into account the ever-changing scene in the ulcer stomach, where constant secretion of acid and intermittent emptying of the stomach made necessary a much greater dosage and more frequent administration than that suggested by studies in vitro.[37] The most glaring deficiency has been the failure to set up proper controls for an objective evaluation of drugs to eliminate or minimize individual differences in interpretation of improvement, and the effect on the physician and patient alike of the power of suggestion stimulated by a new preparation.[39] The measure of symptomatic relief alone is never an adequate or safe yardstick.[40] Although the disappearance of the ulcer crater is a more objective criterion, it is not always a reliable index of healing. The crux of the ulcer problem

remains the inevitability of recurrence in the natural course of the disease. The most important index of the therapeutic effectiveness of any measure — drug, diet or regimen — will be its influence on the rate of recurrence as determined over a period of years, not months. At present no course of medical treatment has been proved to have any significant degree of success in this most important regard.

Calcium Carbonate

Antacids act only on the gastric secretion already formed and are effective only during the period of administration, neutralizing the acid either by reacting with it chemically or by adsorption. Calcium carbonate is one of the oldest of the antacid drugs and still among the most effective.[36, 37, 41, 42] Given in hourly doses of 2 to 4 gm., especially if combined with milk and cream, it maintains the pH of gastric contents at 4.5 to 5.0. Unless the patient is vomiting or subjected to frequent aspiration, this dose will not result in alkalosis. Its constipating effect may be controlled by the addition of varying amounts of magnesium oxide or magnesium carbonate.

Magnesium Preparations

Magnesium oxide, though one of the most effective neutralizers, is used only in conjunction with less potent antacids to counteract their constipating effect, since its own laxative action in the therapeutic range is too great for clinical use. Magnesium trisilicate in tablet form, in doses of 2 to 4 gm. hourly, may have a partially neutralizing effect, though one that is inconstant and often delayed.[36, 37]

Aluminum Preparations

Aluminum hydroxide was one of the first of the preparations introduced to counteract the fear of upsetting the electrolyte balance with the more soluble antacids.[36, 37, 42, 43] With magnesium trisilicate it belongs to the group of colloidal nonreactors whose neutralizing effect is exerted primarily by adsorption of hydrochloric acid. Despite claims to the contrary, a secondary rise in acidity after its use has been observed. Although experiments in vitro indicate a potent neutralizing effect, large doses are required to raise the pH to levels of therapeutic benefit in patients with duodenal ulcer. No adverse clinical reaction resulting from the consequent increase in phosphate excretion has been noted, since the usual bland ulcer diet has an excess of phosphate. In the use of other aluminum preparations the constipating effect of aluminum hydroxide is modified by a combination with various laxatives.

Sodium Carboxymethylcellulose

SCMC (sodium carboxymethylcellulose) varies in consistence after ingestion from a gelatinous mass to a viscous compound, acting as a true buffer while in solution and as an anion-exchange substance in its gel stage, its sodium being substituted for the hydroxide ion.[35-37, 40, 44] In addition it is said to coat the gastric and duodenal mucosa with a protective, tenacious surface. Its cellulose content explains its capacity to act as a bulk laxative. In one series, in which its effectiveness was compared with that of aluminum hydroxide, 61 per cent of the patients remained asymptomatic a year after taking SCMC, as compared with 40 per cent receiving aluminum hydroxide. It is now prescribed as Carmethose in tablets containing 225 mg. of SCMC and 75 mg. of magnesium oxide — half the originally recommended dose.

Mucin

The idea of explaining the pathogenesis of peptic ulcer on the basis of a gastric deficiency of a naturally occurring substance is attractive. The role of mucin in this connection was proposed on the following grounds: mucin is an effective buffer of gastric acid; there is a diminished amount of gastric mucin in patients with peptic ulcer owing to decreased production or increased destruction by mucolytic activity, and this decrease leads to gastric denudation and facilitates mucosal erosions; and commercial preparations of mucin are of therapeutic value in ulcer. Much of the earlier work on which this important position of mucin is based will have to be revised in the light of recent studies by Glass.[45] There are at least three components of gastric mucus: visible surface epithelium mucus, whose tenacious quality makes its removal from the stomach by aspiration for clinical determination difficult; dissolved mucoproteose, which is the dissolution product — and can be measured as an indirect index — of surface epithelium mucus; and dissolved gastric mucoprotein, which is independent of the first two and is derived from the mucoid chief cells in the fundus and body of the stomach. The last two constitute the total dissolved gastric mucin. Any study purporting to show the status of mucin in the stomach must take into account this diversity of mucus composition and the relative amounts of each component. Glass[45] has shown that there is no increase in dissolved mucoproteose and, therefore, no increased destruction of gastric mucin by lysozyme activity. In vivo studies by Wolff and Wolf[46] demonstrated the importance of mucus in maintaining the surface of the gastric mucosa in a relatively neutral environment and, with its tenacious covering, physically protecting it from irritating stimuli. In practice, however, commercial preparations of mucin have been variable and only weakly neutralizing. When it is taken in the form of capsules or granules, the amount necessary to produce any significant neutralization results in large gummy masses unevenly distributed in the stomach. Recently, it has been

combined in tablet form with magnesium trisilicate and aluminum hydroxide as Mucotin[38] and with an anion-exchange resin as Resmicon. It is doubtful whether the effect of these combinations is greater than that of either constituent alone.

Protein Hydrolysates

Protein hydrolysates have been variously praised for their neutralizing power and nutritious content, and criticized for their unpalatability, their tendency to produce a rebound rise in gastric secretion and their unpredictable efficiency in combating acid secretion.[47, 48] Attempts have been made to explain some of these discrepancies on the basis of inadequate concentration of the oral preparation used, and infrequency of administration.[49] The ability of 30 gm. of protein hydrolysate mixed with 30 gm. of dextrimaltose when given hourly to produce adequate neutralization in only half the group of test patients was attributed to the more rapid rate of gastric emptying in patients who failed to respond. When this rate was retarded by atropine, complete neutralization was obtained. The use of a 10 per cent protein hydrolysate in combination with milk was found to give a greater buffering effect than either alone.[50] However, in the average patient with ulcer whose nutritional status is satisfactory, it has not been found necessary to resort to such unpalatable mixtures.

Anion-Exchange Resins

Anion-exchange resins were first suggested for use in peptic ulcer in 1945.[51, 52] Their clinical application is based on their ability to bind the acid radical in the stomach and to release it in the alkaline medium of the small intestine, thus causing no interference with the acid-base equilibrium or mineral balance.[53] The neutralizing qualities are not superior to those of other antacids, though when the resins are given in doses of 1 or 2 gm. hourly, which is much larger than the amount usually prescribed, partial reduction in gastric acidity has been obtained. The side effects observed in such large doses include only nausea and belching.[54] The healing of the ulcer crater with resins is not significantly faster than that observed with aluminum hydroxide, if one considers the psychic effect implicit in any new medication recognized as such by the patient.[55]

Anticholinergic Drugs

In view of the continuity of gastric secretion and the periodic emptying of the stomach, adequate neutralization to be effective in the relief of symptoms and in the healing of the lesion would require almost constant use of bland foods and antacid medication — at times even during the night in patients with duodenal ulcer and excessive nocturnal secretion. Such a regimen would be grossly impractical and would seldom be followed by the patient for long. Ideally, a drug capable of inhibiting gastric secretion of acid would effectively eliminate the ulcer problem regardless of the importance of other factors.[37] To this end the development of anticholinergic drugs has provided the most promising lead though one that is still far from success.

Atropine

Atropine, the oldest drug in this group, acts peripherally to interfere with the responsiveness to acetylcholine at the postganglionic nerve endings.[56] In doses of 1.2 mg. it is capable of producing marked diminution in the rate and amount of acid secretion, as well as slowing the gastric emptying time.[57] In this dosage, it is almost always associated with unpleasant and even toxic symptoms such as tachycardia, dryness of the mouth, blurring of vision and occasionally mental confusion, all of which militate against its clinical usefulness. Doses of the magnitude usually prescribed — namely, 0.5 mg. — are variable in their pharmacologic effect and seldom produce any significant changes in secretion. Its synthetic analogues, Syntropan and Trasentine, are even less effective.

Banthine

Banthine is perhaps the best known of the quaternary amines recently introduced for the treatment of peptic ulcer.[58, 59] In the parasympathetic nervous system it blocks the impulses at the ganglionic synapse as well as at the postganglionic nerve endings, and in larger doses it exerts a similar effect on the ganglionic synapse of the sympathetic nervous system.[60] Its action is more noticeable in slowing the motor activity of the stomach than in diminishing its secretion.[61, 62] Such an alteration of motility may aggravate a complicating pyloric obstruction, and contraindicates its use in chronic constipation and prostatic obstruction. The symptomatic response to this drug has at times been so striking as to mask the persistence of the ulcer crater, whose healing has lagged behind the subjective improvement.[63] It should, therefore, not be relied upon as the sole therapeutic agent but considered as a useful supplement to the usual methods of treatment.[64-67]

There is little choice between atropine and banthine if the former is used in full tolerance dosage, but it is simpler to manipulate the dosage of banthine necessary to obtain the proper anticholinergic effect because of its greater gravimetric dose.[68, 69] The dosage usually recommended is 50 to 100 mg. after meals and at bedtime, but this may have to be modified to suit the individual case.[70, 71] Recurrences and complications have been noted while the drug was being administered, so that it has in no way altered the basic and conventional principles of treatment, in spite of the enthusiasm with which it was first received.[72] As with all anticholinergic

drugs, dryness of the mouth, blurring of vision and tachycardia are frequent associated effects, which in some cases make continued use intolerable to the patient.[37]

Hexamethonium

Hexamethonium iodide and bromide are potent depressors of gastric secretion and motility with the added advantage that they can be given orally.[36, 37, 40] However, the undesirable effects described above in conjunction with other anticholinergic drugs, as well the distressing ones of postural hypotension and syncope, invalidate their usefulness except in bed patients. Moreover, this double effect on gastric secretion and motility, a property of most anticholinergic drugs such as atropine and banthine, may operate to the disadvantage of the patient. The decrease in motility and therefore delay in gastric emptying may counteract the initial lowering of volume and concentration of acid and even result in an actual increase in total volume of the intragastric contents without producing any appreciable elevation of the pH. Even when hexamethonium is used in conjunction with antacids, the neutralizing effect is prolonged in only half the patients.[73]

Tetraethylammonium

TEAC (tetraethylammonium chloride) resembles other anticholinergic drugs in its pharmacology and effect on motility, though it is of benefit only when given parenterally.[74] Its method of administration and the complications of postural hypotension, tenderness at the site of injection and, rarely, intestinal and diaphragmatic paralysis limit its use to patients with severe nocturnal distress but without hypertension or hemorrhage.

Dibuline

Dibuline is a choline derivative used only parenterally and capable of reducing the volume of gastric secretion if given in a dose of 40 mg. every three hours.[75] Any longer interval or smaller dose results in variable responses. A comparable effective dose of 1.0 mg. of atropine produces such toxic effects as to make its clinical use inadvisable. Dibuline given every three hours is of most value in patients whose persistence of symptoms is associated with excessive nocturnal secretion. It is hardly the ideal acid inhibitor for everyday use.

Prantal and Antrenyl

Prantal[76-80] and Antrenyl[81] are two of the newest quaternary compounds, presumably with few intolerable side effects when used in the oral dosage originally recommended — namely, 50 mg. and 5 mg. respectively. However, a dosage schedule at least five times greater was found necessary for prompt relief of ulcer pain, and caused the untoward symptoms of constipation, urinary retention and dryness of the mouth. This sequence of events emphasizes the desirability of an anticholinergic drug with specificity of action on the parasympathetic nervous system limited to its influence on secretion and motility of the stomach. This goal is perhaps impossible to achieve since the actions described are manifestations of the normal pharmacologic action of the drugs on other organs served by the parasympathetic nervous system. At the present writing, no member of this group satisfactorily meets these qualifications though their addition to the medical armamentarium represents a distinct advance that further investigation may follow with profit.[36, 37, 40]

Enterogastrone

Attempts to increase the resistance and regenerating power of gastric and intestinal mucosa have also claimed the attention of many investigators.

Enterogastrone is the name given to the hormone whose formation is induced by the presence of fat in the upper small intestine and that inhibits gastric secretion and motility. It has a protective action in Mann–Williamson dogs against the formation of ulcer when given parenterally, without demonstrating any obvious effect on gastric secretion. This beneficial influence was attributed to an antiulcer factor that increased tissue resistance and induced healing.[82] However, in common with many similar preparations, such as extracts of animal stomach and duodenum (Viodenum and Robuden),[83] it has proved disappointing in man when used orally, and unpredictable and of short duration in its effect on secretion even when given by injection. Thus its beneficial action, if any, does not derive from an antisecretory function. Certainly, when proper controls were instituted, with neither the patient nor the physician aware of what was administered the results were no better than placebos or conventional therapy.[84-88] Perforations have occurred during the course of treatment with enterogastrone.

Urogastrone

Urogastrone, an extract prepared from human urine, resembles enterogastrone in its antisecretory effect when given intravenously to dogs and in its protective action against ulcer formation in Mann–Williamson dogs. Again, this beneficial influence is attributed to a substance in the extract capable of promoting healing of tissue — uroanthalone. However, its use in man has had no favorable action on the rate of recurrence.[36, 37, 40]

Kutrol

Kutrol, an extract from the urine of pregnant mares, reflects the influence of clinical observations that indicate a much higher percentage of peptic ulcers among male patients and the apparently beneficial effect of pregnancy on the natu-

ral course of ulcer.[80] Given in capsule form of 150 mg. four times daily, it produces neither an antacid nor an antisecretory effect. Favorable results have followed its use in previously intractable patients, and it is credited with prolonging the recurrence interval in a third of the patients observed over a twelve-month period.[80] However, not enough time has elapsed for these early encouraging results to have any substantial therapeutic significance.

Eugenol

The rationale for treatment with this preparation is that it stimulates the formation of mucous secretion in the stomach, with its consequent protective effect.[89] Of 14 patients who were given periodic gastric instillations of a 3 per cent eugenol emulsion, 6 were completely relieved, although 3 soon relapsed on a regimen that included no medication and no dietary restrictions. There appeared to be no correlation between the clinical response and the laboratory findings. The conclusion reached was that this particular therapy in the form in which it was administered had no unequivocal effect.[89]

Antihistamines

In view of the normal effect of histamine in evoking gastric secretion rich in acid juice, various preparations of antihistamines[90] have been used, without any substantial favorable result on the symptoms, healing time or rate of recurrence.[91] In certain cases they stimulated gastric secretion.[91]

Chlorophyll

In connection with the recent widespread use of chlorophyll derivatives for almost every condition, it has been recommended for the treatment of peptic ulcer in combination with aluminum hydroxide and magnesium trisilicate.[92] Although the immediate results were good, the experiments were poorly controlled, and there is no evidence that the added chlorophyll gave any result better than that observed with either drug alone.

Tropine

Tropine has been shown to have properties similar to those of atropine and the antihistamines.[93] Given orally every six hours, in amounts of 0.5 to 2.0 mg., it produced symptomatic improvement without any effect on the emptying time of the stomach or on the level of acid gastric juice. In larger amounts it had untoward effects similar to those observed with atropine. The symptomatic results may be attributable to its local anesthetic properties.

(To be concluded)

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MEDICAL INTELLIGENCE

DOCTORS AFIELD

Joseph Ignace Guillotin

JOSEPH GARLAND, M.D.

BOSTON

EVEN as the evil that men are merely said to do lives after them, so the present fame of Dr. Joseph Ignace Guillotin, a physician of Paris, rests on the attachment of his name to an instrument that he did not invent, and his very real contributions to society have been generally forgotten.

Guillotin, a lawyer's son, was born on May 29, 1738, at Saintes; his education at Bordeaux progressed so satisfactorily that he was given at an early age a professorship in the Jesuit College in that city. After a short tenure at Bordeaux he matriculated in 1763 as a medical student in Paris, removing five years later to Rheims, where he obtained his "doctor's hat" somewhat more economically than was possible in the capital. Having returned to Paris he was awarded his official degree in medicine in 1770. Soon after receiving his diploma Guillotin was appointed a *docteur-régent* of the medical faculty — the highest distinction then possible — and became a popular teacher and practitioner.

In 1784, the theory of animal magnetism introduced by Mesmer having achieved a high degree of undesirable notoriety, Guillotin, Lavoissier, Benjamin Franklin and others were chosen by Louis XVI as a commission to investigate Mesmer's therapeutic claims. The report of the commission was unfavorable, and Mesmer was forced to abandon his irregular practices and eventually to leave Paris.

Guillotin became a popular hero in 1788; in that year, in a pamphlet published on December 8, on the eve of the first convocation of the States-General in a hundred and seventy-five years, he expressed his views concerning the political importance and rights of the Third Estate. This pamphlet, considered as one of the political manifestos that went far toward preparing the way for the Revolution, presented the claims of the commons for at least as many representatives in the States-General as were accorded the nobility and the clergy.

The pamphlet, freely circulated and adopted by the six corps of merchants as their official petition, won its case, and Guillotin, as a result, was elected a people's representative for the City of Paris, becoming president of the General Assembly that succeeded the States-General. During this brief period Guillotin — perhaps a euthanasist at heart — insisted that execution by decapitation should no longer be the privilege solely of the upper classes but that all citizens, when it became necessary, should enjoy this form of capital punishment "by a simple mechanism — short, sure and as painless as possible." It was not his thought that the mechanism should become the engine of destruction of a reign of terror.

The machine suggested by Guillotin was far from being a novelty, although for a century it had been in disuse on the Continent. He had apparently obtained his information concerning it from the de-

J.I. GUILLOTIN

Député à l'Assemblée Constituante.

Né à Saintes le 29 Mars 1738.

scription in an anonymous work of an execution that took place at Milan in 1702. Similar decapitating devices had been employed in Scotland, England and Germany, and in Italy since the thirteenth century; an early woodcut represented even St. Matthew as dying through such an agency.

The antiquarian museum of Edinburgh still houses the guillotine known to the hardy Scots as "the maiden," by which the regent Morton lost his head in 1581. The last occasions on which the Scottish maiden delivered a short sharp shock on a big black block were the execution of the Marquis

of Argyll in 1661 and that of his son, the Earl of Argyll, twenty-four years later.

Another macrotome, the Halifax gibbet, was used in Halifax, West Riding, Yorkshire, in the

Petrus Mauleus filium suum ejus justu cum hoste pugnantem obtruncavit.

seventeenth century; in Germany a similar machine was in general use during the Middle Ages under the name of the *Diele*, the *Hobel* or the *Dolabra*. The instrument used in Italy for the execution of nobly born criminals went under the name of *Mannaia*.

Guillotin's suggestion to the Assembly having been accepted, a machine was constructed with which experiments were conducted on cadavers in the hospital of Bicêtre. Another physician, Dr. Antoine Louis, and a German mechanic named Schmidt were responsible for the designing of this piece of apparatus, which was set up for business on the Place de Grève for the execution of the highwayman Pelletier, on April 25, 1792. Louis is said to have suggested as one of his contributions the obliquity of the cutting edge of the knife — a refinement of design that increased its general effectiveness.

Meanwhile Dr. Guillotin had retired from politics with the ending of the General Assembly in 1791. Despite his absence from the scene, however, the machine, which had at first been called *Louisette* or *La Petite Louison*, and later *Mirabelle*, in honor of the orator, Mirabeau, soon became officially known simply as the guillotine.

Dr. Guillotin, a persistently moderate patriot of 1789, abhorred the Reign of Terror and in his retirement denounced Robespierre and protected, when possible, the victims of the Revolution. He was finally arrested and was saved only by the fall of Robespierre from the death by guillotine that is believed by many to have been his fate.

After the Terror Guillotin rose to considerable prominence in his profession, becoming the founder of a scientific society, the Académie de Médecine, that consisted of the surviving members of the old faculty of Paris and a number of physicians of other French faculties. An ardent follower of Jenner, he headed a French committee for the propagation of vaccination. He died on March 26, 1814 "of an anthrax of the left shoulder."

As Victor Hugo said, according to Lutz*: "There are unfortunate men: Columbus could not attach his name to his discovery, and Guillotin could not detach his from his invention." Only it was not even his invention!

*Lutz, F. J. Guillotin. *Internat. M. J.* 16:340-352, 1909.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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CASE 39231

PRESENTATION OF CASE

A seventy-year-old tailor was admitted to the hospital because of progressive weakness of three weeks' duration, and more recently chest pain, agitation and confusion.

Four years previously the patient had been seen at this hospital because of unexplained fever. At that time he gave a history of attacks of chest pain for three years relieved by nitroglycerin, and an electrocardiogram confirmed the presence of coronary-artery disease. Aside from a blood pressure of 170 systolic, 120 diastolic, and a temperature of 99.5°F., the physical examination and laboratory studies were negative. After about a week the temperature reverted to normal, and he was discharged with the diagnosis of hypertension and arteriosclerotic heart disease; no explanation for the fever was found. Since discharge he had had occasional bouts of angina on exertion and excitement. One year before admission, while he was in Florida, a bowel tumor reported as leiomyosarcoma was resected. He had been free of symptoms, however, except for slight constipation, and three weeks before entry a gastrointestinal series and barium-enema examination were reported as negative. At about this time, after an emotional upset, he felt weak and experienced nonradiating substernal pains of short duration. He felt dizzy and had momentary dyspnea. His physician found a regular pulse of 75, and a blood pressure of 160 systolic, 100 diastolic. There was no venous distention, but the liver edge was felt two fingerbreadths below the costal margin. An electrocardiogram showed changes suggesting further infarction. He continued to be weak and lethargic until four days before admission, when he had chest pain, radiating to the arms and shoulders, that was relieved by a hypodermic medication. He was ambulatory on the following day but continued to feel weak. On the next day he became confused, aphasic and agitated, was unable to co-ordinate his arms and legs, and was incontinent of urine but not of feces. During this time he had had excessive thirst.

Physical examination showed a dehydrated, agitated, confused man who did not respond to directions. The pupils were constricted and equal, and the neck was supple. The apical rate was 80 and regular, with an occasional premature beat. The cardiac sounds were fair, with an inconstant gallop. There were no murmurs. The lungs were clear; the liver edge was felt two fingerbreadths below the costal margin. Speech was limited to moans. The extraocular muscles were normal but could not be examined through their full range because the patient was unable to co-operate. The corneal reflexes were negative; pinpricks were felt bilaterally. There was slight facial weakness on the right. The gag reflex was active, and the tongue motions normal. All passive motions were resisted. The deep tendon reflexes were slightly more active on the right; the Hoffmann sign was positive. There was no ankle clonus; the plantar response was questionably extensor on the right and flexor on the left. There was no gross weakness of any extremity. The carotid pulsations were present bilaterally.

The temperature was 99.8°F., the pulse 90, and the respirations 20. The blood pressure was 190 systolic, 114 diastolic.

Shortly after admission, the patient became ashen gray and had periods of apnea lasting forty-five seconds, alternating with fifteen-second periods of vigorous respirations. During the apneic period he had twitchings of the left leg followed by clonus lasting fifteen seconds. Twitchings were also seen around the left eye. The eyes deviated to the right; the right arm and leg were markedly spastic, but there was no change in the Hoffmann or plantar responses. Because of apnea, aminophylline was given, and a generalized convulsion followed.

Examination of the blood showed a hemoglobin of 15.5 gm. per 100 cc., and a white-cell count of 21,700, with 89 per cent neutrophils, 5 per cent lymphocytes and 6 per cent monocytes. The blood sugar was 155 mg., the nonprotein nitrogen 56 mg., and the phosphatase 25.3 units per 100 cc.; the carbon dioxide was 27 milliequiv., the chloride 92 milliequiv., the sodium 139 milliequiv., and the potassium 5.5 milliequiv. per liter. A blood Hinton test was negative. A lumbar puncture yielded clear, colorless spinal fluid, with a normal pressure and normal respiratory dynamics. The spinal fluid contained 1 lymphocyte per cubic millimeter and 52 mg. per 100 cc. of protein and gave a gold-sol curve of 0111322110. An electrocardiogram was highly suggestive of a recent anterior myocardial infarct and showed changes consistent with an old posterior infarct.

In the hospital the seizures were treated with Dilantin and subsided, but the patient became comatose. All extremities became flaccid. The

pupils remained fixed. Otherwise, the neurologic findings remained unchanged. The blood pressure dropped to 80 systolic, 60 diastolic. Coma deepened, the temperature rose to 104°F., and the patient died on the ninth hospital day.

Differential Diagnosis

Dr. Earle M. Chapman*: It seems to me that this patient suffered at the age of seventy from what I should call a widespread vascular disease that involved primarily the heart with a coronary occlusion and myocardial infarction, first of the posterior wall and in his final illness of the anterior wall. Along with this he had hypertension until the final episode, when the blood pressure dropped; then he must have had some vascular disease in the kidneys, which was probably a terminal event, because the nonprotein nitrogen rose to 56 mg. per 100 cc.

I wondered about disease in the liver, but there was little to guide me from the standpoint of liver function except the isolated finding of an alkaline phosphatase of 25 units, which is consistent with congestive heart failure and stasis in the liver — perhaps a stasis in the liver of longer standing than was indicated in the history. Of course, the facts that the leiomyosarcoma had been removed from the bowel and the liver edge was palpable two fingerbreadths below the costal margin suggest that the liver might have harbored metastases.

What else was involved? The whole final episode suggests that he had some type of cerebrovascular accident; however, the neurologic evidence and the facts in the history do not permit me to localize clearly the process in the cerebrum. The vascular lesions in the brain that I particularly think of are hemorrhage, thrombosis and embolism. At one point I was tempted to suspect that along with the myocardial infarct there was a mural thrombus; perhaps it was even infected so that there was an acute endocarditis and parts of the thrombus dislodged and spread widely throughout the brain substance. That would explain why at entry the white-cell count was 21,000. After thinking the case over, I concluded that the terminal episode could best be related to thrombosis or embolism — I believe there is a fifty-fifty chance of either — in the basilar artery. Kubik and Adams† described very clearly the syndrome of basilar-artery thrombosis to which this man's symptoms and signs seemed to conform very well. He had a change in the state of consciousness and inability to speak; in addition he had contracted but equal pupils and finally facial palsy, which is another characteristic of this syndrome. Finally, there is an interval during which the infarction of the pons becomes complete. In the terminal stages, the patients nearly always have a hemiplegia or even a quadriplegia and high fever. With this syndrome of basilar-artery thrombosis or embolism with infarction of the pons the spinal-fluid cell count and the pressure are usually normal whereas the blood white-cell count is usually elevated.

Thus, the order of events and deterioration in this man's health, I think, can all be explained on a vascular basis. One thing that does concern me is whether he had some form of liver failure. He had circulatory failure and renal failure and also some liver failure, but was the liver failure predominant? I do not believe it was because there was no sign of jaundice and no record that any further liver studies had been done; the high alkaline phosphatase disturbs me and makes me wonder whether he had widespread metastases in the liver. The whole syndrome could then be called cholemia, but I shall rule it out.

Dr. Daniel S. Ellis: You mentioned the possibility of metastatic disease to the liver; do you think the patient may have had a cerebral metastasis to explain this?

Dr. Chapman: I doubt it, but I suppose it is possible.

Dr. William H. Timberlake: How do you explain the focal seizure in basilar-artery thrombosis?

Dr. Chapman: Seizures have been frequently described. Dr. Charles S. Kubik mentioned that it had occurred in some of his 18 cases.

Dr. Conger Williams: One important point about the convulsions was not mentioned in the history. These seizures were true Jacksonian convulsions of focal origin that became generalized.

When the patient was admitted to the hospital I wondered about metastases to the liver, but the question of hepatic coma came as an afterthought; one of the house staff brought it up first. Although seizures are common in hepatic coma I doubt if they are ever Jacksonian. Another thing that concerned us as the syndrome developed and the state of unconsciousness became deeper and deeper was the possibility of subdural hematoma or something of that sort that could be operated on. Dr. Timberlake was asked to see the patient.

Dr. Timberlake: The speech difficulty was difficult to evaluate because he did not speak while he was here; the history was not clear but suggested that it was aphasic. He spoke some words clearly, and then at the end of the sentence "got lost." Apparently, there was no telegraphic speech. The seizures, as Dr. Williams has indicated, were clearly Jacksonian. They started in the foot, did not involve the arm and then appeared in the face. We wondered whether another embolus had infarcted the arm area, completely paralyzing it so that it could not respond to the spreading seizure activity. The weakness of the face seemed to have been of upper-motor-neuron type. The remaining cranial nerves seemed normal. We did not believe that this was a basilar-artery thrombosis because we saw

*Physician, Massachusetts General Hospital.

†Kubik, C. S., and Adams, R. D. Occlusion of basilar artery: clinical and pathological study. *Brain* 69:73-121, 1946.

no evidence of involvement of the lower motor-neuron cranial nerve, because of the focal seizures and because of the apparently aphasic type of speech disorder. An electroencephalogram made after the onset of the seizures showed high-voltage slow waves, focal in the right frontal and central region, with the greatest disturbance in the right central region. The weakness at the end was a generalized paralysis reflecting the coma and not strictly a quadriplegia. We placed the lesion higher than the brain stem. We thought that, as a result of a previous cardiac infarction, a mural thrombus had developed and that from this emboli had broken off, causing infarcts first in one and then in the other cerebral hemisphere.

Clinical Diagnoses

Cerebral emboli.
Hypertensive arteriosclerotic heart disease, with auricular fibrillation.
?Recent myocardial infarct.

Dr. Earle M. Chapman's Diagnoses

Coronary occlusion, with myocardial infarction.
Basilar-artery occlusion, with infarction of pons.

Anatomical Diagnoses

Coronary occlusions, with myocardial infarction, old.
Mural thrombus, old, left ventricle.
Cerebral embolus, with infarction of right temporal and parietal lobes, recent.
(Leiomyosarcoma of jejunum), with extensive metastases to liver.
(Jaundice.)
Confluent bronchopneumonia, severe, right upper and lower lobes.
Hypertensive heart disease with cardiomegaly (weight of heart, 480 gm.).

Pathological Discussion

Dr. Edgar B. Taft: This patient's primary disease was severe atherosclerosis of the coronary arteries. At autopsy the heart was enlarged, weighing 480 gm. A large part of the myocardium of the left ventricle at the apex and septum was replaced by scar tissue, with aneurysmal dilatation of the area. There was an old mural thrombus over the endocardium in the aneurysm. There were old occlusions of the extremely sclerotic coronary arteries, one in the left anterior descending branch 2 cm. from its origin and one in the right coronary branch 6 cm. from its origin. The atria contained no mural thrombi. There was no evidence, grossly or microscopically, of recent infarction.

The neurologic signs and symptoms were explained by a large area of recent infarction in the right temporal and parietal lobes. The cerebral vessels were remarkably free of atherosclerosis. An embolus was searched for, but none was found.

There was a severe bronchopneumonia of the right upper and lower lobes that was confluent in some areas, and bronchiectasis of both lower lobes. However, no evidence of heart failure was observed either in the lungs or elsewhere.

The most surprising finding in this autopsy — and it is hard to believe that this was not an important factor in the patient's terminal episode — was the liver, which was almost completely replaced by nodules of metastatic leiomyosarcoma. These certainly explain the liver enlargement, the elevated alkaline phosphatase and the slight jaundice that this patient had at autopsy. There was no evidence of residual tumor in the bowel, and the end-to-end anastomosis of the mid-jejunum was well healed.

Dr. Edward P. Richardson, Jr.: Although it was carefully looked for, we were unable to demonstrate a lesion in the left cerebral hemisphere to account for the initial disturbance of speech and right-sided neurologic signs. However, the left-sided focal seizures fit in well with the infarction seen in the right temporoparietal region. The most plausible explanation of the cerebral infarct in this case is cerebral embolism, and the inability to find an embolus on gross dissection of the brain does not rule this out.

It must be kept in mind that convulsive seizures are a rare accompaniment of occlusion of the basilar artery with infarction of the pons, and are not a part of the syndrome associated with that condition. There may, however, be attacks of generalized extensor rigidity thought to represent decerebrate rigidity. Furthermore, focal convulsions in hepatic failure should always lead to the strong suspicion that there is a focal cerebral lesion in addition to any alteration of brain function associated with the cholemic state.

CASE 39232

Presentation of Case

A twenty-three-year-old single woman came to the Emergency Ward shortly after midnight because of abdominal pain.

Five days before admission after washing her car, the patient suddenly experienced pain in the left upper quadrant of the abdomen that was moderately severe and steady but was not associated with nausea or any other symptoms. A short time later she ate a large lunch. By the following day the pain had become upper abdominal in location, being more severe in the right upper quadrant, less severe in the epigastrium, and virtually absent in the left upper quadrant. It was steady, not crampy, did not radiate to the back or shoulders, and was tolerable until the day before entry, when it became severe. Its character and distribution did not change. She had some nausea but no vomiting. Before this she had continued to work and eat meals. She had been

having two or three soft to watery stools daily since the onset of her symptoms but she ascribed this to a laxative that she had taken on the first day.

She denied any history of intolerance to fatty foods or other symptoms and had never had a similar episode in the past.

Physical examination showed a well developed and well nourished woman who appeared moderately ill. She walked bent over because of pain. The heart and lungs were normal. In the abdomen there was guarding of the right upper quadrant and epigastrium, with marked tenderness. There were

FIGURE 1.

no masses or enlarged organs; peristaltic sounds were not increased. The rest of the examination, including the rectal examination, was negative.

The temperature was 100.2°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

A urinalysis was negative. Examination of the blood revealed a hemoglobin of 13 gm. per 100 cc. and a white-cell count of 17,000, with 87 per cent neutrophils, 9 per cent lymphocytes, 3 per cent monocytes and 1 per cent basophils. A stool specimen was guaiac negative. A plain film of the abdomen disclosed a large amount of gas in the small bowel in the left side of the abdomen, with no abnormal distention of the bowel. Gas was also present in the right side of the abdomen, probably in the large bowel (Fig. 1). There were no obvious opaque calculi.

About six hours after admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. GEORGE L. NARDI*: When I read this case it seemed quite straightforward and simple. It was simple also in terms of management because this was a surgical problem in which, even with two or three diagnoses, the treatment would be the same. I hope this turns out to be a true statement.

In view of the age, the short duration of the disease, the fever, the findings and the elevated white-cell count, I think the patient had an inflammatory condition that was limited to the upper half of the abdomen. There are numerous rare conditions that I shall mention in passing but shall not take too seriously. The confusing feature to me is the onset of distress in the left side of the abdomen. She may have had a renal calculus in the left kidney; if that were so, that would bring up the differential diagnosis of hyperparathyroidism, cystinuria and pyelonephritis. She may have had a ruptured spleen. Hiatus hernia could give symptoms something like this initially. Although all those conditions could have given her trouble on the left side I shall not consider any of them seriously.

The diagnoses that come to my mind are acute cholecystitis and perforated peptic ulcer. In addition I should like to mention acute appendicitis; about two years ago I saw a girl with right-upper-quadrant pain who was operated on with a diagnosis of perforated ulcer; she had acute appendicitis, with an incompletely rotated cecum. Another possibility, a condition that occurs more often than we realize, is right-sided pneumonia. I have taken out a gall bladder in such a case, which the pathologists kindly called chronic cholecystitis; there have been other cases in which the pneumonia was not recognized initially.

May I see the x-ray films?

DR. JOHN F. GIBBONS: Only one film was made after entry; unfortunately, an upright film of the abdomen was not taken. In this film taken with the patient supine gas is present in a normal-looking stomach and in many loops of the small bowel that do not appear dilated; moreover, gas has collected in the right upper quadrant, apparently in the cecum, which also contains some fecal material, and possibly in the proximal transverse colon although I cannot be sure that that is not a dilated loop of small bowel. A striking feature is that the small-bowel loops are concentrated in the midportion of the abdomen, which suggests that there is fluid in the abdominal cavity upon which the gas-filled loops are floating (Fig. 1). The psoas-muscle shadows, however, and the properitoneal fat lines are well delineated so that even though there is fluid

*Assistant in surgery, Massachusetts General Hospital.

in the abdomen one may assume that there is no inflammation of the properitoneal fat, which usually results from peritonitis. There is no evidence of small-bowel obstruction. This appearance would more likely be the result of a paralytic ileus. The spleen is well outlined and appears normal; the liver appears to be enlarged. The left kidney shadow can be outlined but the right cannot be; this may be due to material in the gut overlying the kidney or possibly to edema around the capsule of the kidney.

DR. NARDI: The presence of gas in the small bowel, whether the bowel is called distended or not, suggests small-bowel obstruction to the surgeon. The question is, Was it paralytic or was it organic? In the absence of crampy abdominal pain and without previous surgery it seems quite likely that this was ileus rather than organic obstruction. In addition the patient had diarrhea and gas in the large bowel so I should not suspect any organic intestinal obstruction.

I should like to run down a few of the other symptoms to see if they give me any clue. The patient had soft, watery stools for several days, probably as a result of the laxative that she had taken. There are all sorts of things that a sentence like this makes me suspect. She could have had food poisoning or the early symptoms of hepatitis. About five years ago we explored an acute abdomen and found nothing; about twenty-four hours after operation the patient blossomed out with jaundice and the full-blown picture of infectious hepatitis. Although that is a possibility I hardly think it is a likely one.

I should like to go back to my two original diagnoses, cholecystitis and perforating ulcer. Frankly, the x-ray picture swings me more to the perforated ulcer. The absence of gallstones, and the story of several days of pain with sudden exacerbation, raises the question of peritonitis. I do not think I should consider tuberculous peritonitis or gonorrheal peritonitis, which sometimes produce right-upper-quadrant symptoms.

I am inclined to put a perforated peptic ulcer as my first choice. Can I decide where the ulcer was? Dr. Gibbons, do you think such a small amount of gas here in the stomach, with so much lower down, could be suggestive of a gastric perforation?

DR. GIBBONS: I do not know whether it has or has not any significance.

DR. NARDI: Do you know what percentage of patients with perforated ulcer in this hospital have free air under the diaphragm?

DR. GIBBONS: I think the figure is probably around 30 per cent. On this film one cannot say that there is no free air, since it is not taken in a position where free air might rise to a place where one could recognize it.

DR. NARDI: In the literature various figures between 25 and 50 per cent are cited, but I daresay not much faith is put in this, for a fair number of patients with symptoms more typical of perforated ulcer than the patient under discussion are operated upon without preliminary x-ray studies. Gastric ulcers occur more frequently in females than males, but the incidence of duodenal ulcer is much higher in young folks. I am therefore inclined to say that this patient had a perforated duodenal ulcer statistically. However, the initial left-sided pain could be better explained by a gastric ulcer on the posterior wall of the stomach. Perforation of such an ulcer could have flooded the lesser omental sac and started off the left-sided symptoms.

DR. ALLAN M. BUTLER: Why, with an acute abdomen and the findings in the plain x-ray films of the abdomen, did not the radiologist follow up with other films that were better?

DR. GIBBONS: I do not know the sequence of events but assume that the patient was brought to the operating room without further delay. I, too, should like to see a film taken in the erect position before that was done.

CLINICAL DIAGNOSIS

Acute cholecystitis.
?Duodenal ulcer.

DR. GEORGE L. NARDI'S DIAGNOSIS

Perforated duodenal ulcer.

ANATOMICAL DIAGNOSIS

Perforated gastric ulcer.

PATHOLOGICAL DISCUSSION

DR. ROBERT H. FENNELL, JR.: Dr. Burland, you operated on this patient; would you tell us your findings?

DR. GEORGE R. BURLAND: When the peritoneal cavity was opened, an inflammatory mass immediately presented. This did not involve the gall bladder, which was normal, but was located on the greater curvature of the stomach 3 cm. from the pylorus — obviously, a perforated gastric ulcer. The perforation was well sealed off with omentum and was not explored further. One portion of loose, infarcted omentum was removed, and fresh omentum tacked up to the stomach. The gastric wall in the region of the perforation was typical of an active ulceration — chickened, edematous and friable.

DR. FENNELL: The omentum showed only hemorrhage and necrosis. There was no evidence of peptic digestion of the fragment. I suppose that the onset of pain five days before admission and its location in the left upper quadrant was due to escaped fluid that entered the lesser omental sac as Dr. Nardi suggested.

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"PHYSICIAN MINUS PHYSIC"

The basic element in the doctor-patient relation is the legal and moral requirement that the physician exercise medical skill and judgment equal to accepted standards in his community. In discharging this obligation most physicians also realize the effect of the patient's emotional reactions and physical environment on his illness. Still another component of the doctor-patient relation that has not been so widely accepted may be defined as the physician's spiritual responsibility to the patient and his family. This may seem at first thought to be the exclusive province of the minister or priest, but in fact the physician is also in a particularly logical position to minister to his patient's spiritual needs. He has the patient's confidence, he sees him frequently, and the patient is already looking to him for physical help. Patients more readily listen to their doctors than to almost anyone else, and for this reason, whether he realizes it or not, every physician has a tremendous influence on the adjustment to life of his patients.

The pressure and tensions of chronic and severe illness or of tragedy and bereavement do not leave people as they found them. Human beings must either grow or shrink under their impact. Every physician sees patients who, because of one or more of these factors, become self-centered, querulous and difficult. He also sees people who make illness or tragedy the means of gaining in understanding, unselfishness and love of others. Few physicians perhaps realize that they themselves are often the ones who determine which of these courses a patient will follow; yet the physician is not fulfilling his entire obligation to his patients and their families unless he recognizes this fact and does all in his power to help them grow out of the small and selfish environment that illness naturally creates. He must help them to develop spiritually, not in spite of but because of the illness. Only when he does this in addition to his medical care can he be truly satisfied.

To help his patients in this way, the physician must have compassion for his fellow men large enough to encompass all who come to him. He must also have or must cultivate a philosophy and a faith in it that is sufficiently strong to lift the patient out of himself to a position from which he views his troubles with a true perspective.

The actual method by which spiritual help is given will have wide variations. Sometimes, it will be simply by sympathetic interest — letting the patient talk himself into a healthier point of view. At others, it will mean sitting down and discussing philosophy or religion with him until he is able to think less selfishly. And on still other occasions, the patient must be confronted with a sudden challenge, a figurative slap in the face — a manner of shock treatment. But whatever method is used in any particular case, the desire to help should be the motivating force and anything done or said to the patient should be the servant of that wish.

Perhaps what has been described is the sort of thing the old-fashioned family doctor did so well. He was not able to prevent or cure many of the diseases with which the modern physician copes so easily. Yet he brought his patients love, giving them courage and a respite from worry that were important factors in helping them fight their disease. Somehow, at his less giddy tempo, he found the time to lift them out of themselves and to give them the spiritual strength they so badly needed. The respect and affection that his patients in turn gave him are adequate testimony to the importance of what he did for them.

The answer to any present lack of this sympathy and understanding lies in the individual physician, in his awareness of the situation and in his willingness to do something about it. This takes time and patience. It is difficult; it requires all his tact and understanding. But it is worth all the trouble, for the result is loyalty, gratitude and an increase in his own spiritual development.

THE FAT OF THE LAND

Despite evidence that a counterclockwise philosophy still exists behind the iron curtain, where fashions even in body contour may be dictated by dictators, an increased concern over increased poundage seems to have affected the American people. Perhaps it is a reaction to the reproach that they still prefer to invest the national income in butter rather than bullets; perhaps it is a real concern over the unhappy relations that are generally supposed to exist between obesity and health, longevity, mobility, levitation — except in water — and emotional stability.

The general tendency is to discount the adjuration of Caesar shortly before his taking off and to accept leanness of body as something desirable, indicating neither excessive cerebration nor a dangerous attitude toward one's fellow man. Accepting as a fact that most people eat more than they need and that many of them, instead of eating only to live, appear to eat to live only to eat, this growing consciousness of another of the important facts of life should meet with universal approval.

A source of information no less authoritative than a Gallup poll has announced that 34,000,000 of Dr. Gallup's countrymen — 45 per cent of the women and 25 per cent of the men — admit their excessive avoirdupois, and the removal of it by whatever method is most available seems to have become the latest fad.

Such a willingness on the part of the public to acknowledge this common problem and to face up to it is naturally gratifying to those who recognize the clinical and scientific problems that obesity presents, and the scientific basis on which its control must rest. Obesity was therefore made the subject of a half day of lectures and a luncheon panel at the New England Postgraduate Assembly last October, and the *Journal* has departed from its usual custom of trying to serve a balanced diet in its content, by devoting most of this issue to a symposium on obesity based on the material presented on that occasion.

Pennington's "Reorientation on Obesity" presents almost dialectically an elaboration of certain theories regarding food metabolism, and the theory that, given the right road to follow, one may eat his way to slimness has its attractive features. The other parts of the symposium, on "Lipogenesis" by Gurin, "Health and Obesity" by Barr, "Relation of Obesity to Longevity" by Dublin, and "The Psychology of Overeating" by Brosin, turn this experiment in banting into a pretty balanced meal after all.

ARGONNE CANCER RESEARCH HOSPITAL

The Argonne Cancer Research Hospital, the first institution especially designed and equipped to use all known radiation sources for the study of cancer, has been opened and put into operation. Built at a cost of $4,200,000 in funds of the Atomic Energy Commission, it will be operated for the Atomic Energy Commission by the University of Chicago as part of its cancer research center, under the direction of Dr. Leon O. Jacobson, professor of medicine. Facilities of the hospital are available to the Argonne National Laboratory and the 32 universities and other research institutions of the Midwest that are participating members of the Laboratory.

This new hospital greatly strengthens the cancer program of the Atomic Energy Commission, al-

ready implemented by adapted hospital facilities at Brookhaven and Oak Ridge.

As new scientific tools are found, people look to the scientists to evaluate those tools in terms of human welfare. That evaluation in the field of cancer is one of the major purposes of this hospital, and it is symbolic of modern medicine that it does not stand alone. It is physically a portion of a larger hospital, a medical school and a great university and is intellectually a link between the medical school and the Argonne National Laboratory of the Atomic Energy Commission, bringing to the sufferers from cancer the means of diagnosing and treating the diseases that have already been discovered, and offering the hope of new means. Just as this hospital is linked with others, so are the problems of cancer — its varied causes, some known, some unknown, its recognition and its cures — linked to the complex problems of growth, differentiation and organization of cells.

It is natural that the Atomic Energy Commission should be interested in cancer. The oldest occupational cancer known to man, which developed in the lungs of the miners of Schneeberg and Joachimsthal, was due to the radioactivity liberated by the uranium and radium in the ores. The skin cancers, the leukemias of the early radiologists and the leukemias present today in some of the survivors of Hiroshima and Nagasaki are further vivid reminders that uncontrolled radiation can cause cancer, just as hundreds of people now living can attest to the fact that controlled radiation cures cancer.

The Argonne hospital is eight floors in height, with two of the floors below ground, where the earth will help shield radiation. Only two of the floors are for patient care, 56 beds being provided. The rest of the building houses numerous radiation devices and laboratories. Equipment includes powerful radiation sources such as a Van de Graaff generator, a 50,000,000-volt linear accelerator and a rotating cobalt "bomb," as well as standard x-ray devices. The hospital also has the most extensive and modern provision for safe use of the radioisotopes produced by atomic piles.

The hospital provides facilities for clinical investigation, not for routine medical care, to determine how radioactive materials and other sources of radiant energy can best be used in cancer diagnosis and therapy. Near the Argonne National Laboratory and partly staffed by members of that Laboratory, the hospital will afford its patients newest developments in atomic energy. The Atomic Energy Commission has found that this type of co-operative effort in clinical cancer research has been of great advantage both at the Oak Ridge Cancer Hospital, with its affiliated universities in the South, and at the Brookhaven Hospital, with its associated universities in the East.

Directly related to effective care of patients and the development of new and improved methods of treatment is the training of the highly skilled personnel needed for the complex procedures. This training will be provided and will serve to disseminate the knowledge gained here. In addition, some members of the permanent staff may be appointed from the staffs of participating institutions.

This approach to cancer research gives opportunity for the effective development of new advances in the field of cancer and provides a means by which the governmental facilities may be made available to the staffs of both private and state universities, to speed the potential applications of atomic energy for the benefit of the patient with cancer.

SPAD WAGON

CLINICAL hypoxia or shortness of oxygen is the term currently recommended by SPAD (the Society for the Prevention of Asphyxial Death, Incorporated) to replace the more familiar, more calamitous and less correct word anoxia, meaning relatively if not totally without oxygen.

SPAD, which has been in existence since 1947 and is now housed in the building of the New York Academy of Sciences, is very largely the result of the unflagging interest and industry of its founder, Dr. Paluel J. Flagg. Not only has SPAD, in these six years, presented 81 courses in laryngoscopy and intubation in various parts of the country, but it has advanced more than 200 scholarships (half of which still await sponsors), and has developed the SPAD wagon, a completely equipped station wagon for the transportation of the unconscious patient.

The first SPAD wagon was activated by the United States Public Health Service Marine Hospital of Staten Island; the Jones Beach Park Commission "Panel Truck SPAD Wagon," with 4-wheel drive, was on duty last summer.

Since clinical hypoxia cuts, as is now apparent, "across the entire field of the practice of medicine," it is suggested that the movement to include it in the curriculums of medical schools "be sponsored by departments of thoracic surgery assisted by anesthesiologists."

Dr. Leigh's well-written thesis, entitled "Respiration Subservient to Nutrition," has been published in a pamphlet, and is deserving of an extensive sale.

Boston M. & S. J. *June 8, 1853*

MASSACHUSETTS MEDICAL SOCIETY

LOCAL REGISTRATION

Physicians of Massachusetts who are about to enter practice or may contemplate changing their main office from one municipality to another are reminded of the following regulation (Chapter 112, Section 8, of the *General Laws*), with which they must comply. Failure to be thus recorded means that the physician may be deprived of the protection that the law provides for those legally qualified to practice.

No person shall enter upon, or continue in, the practice of medicine within the commonwealth until he has presented to the clerk of the town where he has, or intends to have, an office or his usual place of business, his certificate of registration as a physician in the commonwealth, or, if it is lost, a certified statement issued by the board, setting forth all the material facts in the original certificate, and a fee of twenty-five cents (now increased to one dollar). Thereupon the clerk shall record the name of the owner of said certificate or certified statement, together with the date of record, upon blanks approved by the board, said blanks to be so arranged that a duplicate carbon shall be made at the time of the original record. He shall keep the original as a part of his official records and it shall be open to public inspection. He shall, within twenty-four hours after such recording, forward the duplicate to the board. Whoever practices or attempts to practice medicine without complying with this section, or whoever submits to a town clerk a false or fraudulent certificate or certified statement, shall be punished by a fine of not less than five nor more than one hundred dollars; and any town clerk who refuses or neglects to comply with this section shall be punished by a fine of not less than five nor more than ten dollars.

ROBERT W. BUCK, M.D.
Secretary

DEATH

SAWYER — Alpha R. Sawyer, M.D., of Lexington, died on May 13. He was in his seventy-second year.

Dr. Sawyer received his degree from McGill University Faculty of Medicine in 1905. He was a member of the American Urological Association and of the Boston Urological Society.

He is survived by his widow, a son, a daughter, five grandchildren and a sister.

CORRESPONDENCE

REGARDING COLOR CHARTS

To the Editor: I have found the visual aid described in the article, "Practical Use of Color in Clinical Diagnosis," in the April 23 issue of the *Journal*, useful and have been employing it for many years. However it is hardly necessary to resort to the cutting and pasting described. Any paint or hardware store has manufacturers' paint-color charts, which are free for the asking.

ELMER A. KLEEFIELD, M.D.

Forest Hills, New York

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Pharmacology in Clinical Practice. By Harry Beckman, M.D., director, departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, and consulting physician, Milwaukee County General Hospital and Columbia Hospital, Milwaukee. 8°, cloth, 839 pp., with 150 illustrations. Philadelphia: W. B. Saunders Company, 1952. $12.50.

Dr. Beckman has written this new book with the intention that it will succeed his well known work, published twenty-two years ago, *Treatment in General Practice*. The text is divided into two parts: clinical use of drugs; and drug data. The subjects are arranged alphabetically and cover all the specialties in medicine, including dentistry. The second part constitutes a compendium of drugs and is intended for reference purposes. Bibliographic notes are appended to the chapters, and the publishing is excellent. The book is recommended for all medical libraries.

Brain Surgeon: The autobiography of William Sharpe. 8°, cloth, 271 pp. New York: The Viking Press, 1952. $3.75.

Dr. Sharpe, having reached his seventieth year, has written an interesting and entertaining story of his life from boyhood to maturity. He tells of his trips to China, where he received $50,000 (equivalent in United States currency) as an unsolicited fee for a single operation, to Russia, where he delivered lectures on neurosurgery, and to Argentina, where he was responsible for the founding of the Pan-American Medical Association and the Pan-American Hospital. This biography should be in all collections on medical history.

Bacterial and Mycotic Infections of Man. Edited by René J. Dubos, Ph.D., The Rockefeller Institute for Medical Research. Second edition. 4°, cloth, 886 pp., with 98 illustrations. Philadelphia: J. B. Lippincott Company, 1952. $7.50.

The first edition of this reference book was published in 1948. Although the organization of the material in this second edition has not been changed, it has been revised, and much of the text rewritten by the thirty-seven collaborators and brought up to date. The voluminous literature on the subject has been evaluated, and bibliographies have been appended to the chapters. There are extensive indexes of authors and subjects, and the publishing is excellent. The low price for this type of volume must be due to subsidization, forming a welcome present to the medical profession. The book is recommended for all medical libraries.

Spanish-English Chemical and Medical Dictionary: Comprising terms employed in medicine, biochemistry, surgery, dentistry, veterinary medicine, biology, pharmacy, allied sciences and related scientific equipment. By Morris Goldberg. 8°, cloth, 605 pp. New York: McGraw-Hill Book Company, 1952. $17.50.

This new Spanish dictionary by a qualified expert is most welcome. This volume, which is a companion to his English-Spanish part, published in 1947, is based on the author's experience of eighteen years as a translator. The publishing is good, and the book is recommended for all medical libraries.

Electrocardiography in Practice. By Ashton Graybiel, M.D., captain, Medical Corps, United States Navy, and director of research, United States Navy, and director of research, United States Naval School of Aviation Medicine, Pensacola, Florida; Paul D. White, M.D., executive director, National Advisory Heart Council, and consultant in medicine, Massachusetts General Hospital; Louise Wheeler, A.M., executive secretary, Cardiac Laboratory, Massachusetts General Hospital; and Conger Williams, M.D., instructor in medicine, Harvard Medical School, and associate physician, Massachusetts General Hospital. Third edition. 4°, cloth, 378 pp., with 294 illustrations. Philadelphia: W. B. Saunders Company, 1952. $10.00.

The authors have entirely rewritten this new edition of a standard book to bring it up to date since the publication of the last edition in 1946. It includes a discussion of the so-called unipolar leads, both limb and precordial, and of vectorcardiography. It is not intended as a textbook, the primary objective being to provide an atlas of electrocardiograms for the physician. There is a good index, and the volume is well published.

Essentials of General Anaesthesia. By R. R. Macintosh, M.A., M.D., F.R.C.S., D.A., Nuffield Professor of Anaesthetics, University of Oxford, civilian consultant in anesthetics to the Royal Air Force, anesthetist, United Oxford Hospitals, examiner for the D. A., and fellow of the faculty of anesthetists, Royal College of Surgeons; and Freda B. Bannister, M.A., M.D., D.A., consultant anesthetist, Wolverhampton Group of Hospitals, Birmingham Regional Hospital Board, and fellow of the faculty of anesthetists, Royal College of Surgeons. Fifth edition. 8°, cloth, 378 pp., with 247 illustrations by Miss M. C. McLarty. Oxford, England: Blackwell Scientific Publications, 1952. $8.00. (Distributed by Charles C Thomas, Springfield, Illinois.)

This new edition of a standard manual, first published in 1940 and republished six times, has been revised by Dr. Bannister. A chapter on curare and other muscle relaxants has been added. Throughout the text reference is made to the pertinent literature, and lists of references are appended to the various chapters. There are indexes of authors and subjects; the publishing is excellent.

Circulatory Dynamics: Physiologic studies. By Carl J. Wiggers, M.D., Sc.D., professor of physiology, and director, Department of Physiology, Western Reserve University School of Medicine. 8°, cloth, 107 pp., with 44 illustrations. New York, New York: Grune and Stratton, 1952. $4.00. Modern Medical Monographs 4.

Dr. Wiggers, a recognized authority on circulatory physiology, presents in this small book three lectures based on his experience of forty years. He discusses basic hemodynamic principles in the interpretation of circulatory disorders, determinants of cardiac performance and dynamics of ventricular contraction under abnormal conditions. There is a bibliography of fifty-five titles and a good index.

Textbook of Gynecology. By Emil Novak, M.D., gynecologist-in-chief, Bon Secours and St. Agnes hospitals, Baltimore; and Edmund R. Novak, M.D., instructor in gynecology, Johns Hopkins University School of Medicine, and gynecologist, Johns Hopkins, Bon Secours, St. Agnes and Union Memorial hospitals, Baltimore. Fourth edition. 8°, cloth, 800 pp., with 523 illustrations. Baltimore: Williams and Wilkins Company, 1952. $9.00.

In this new edition Dr. Novak has thoroughly revised and brought up to date his standard book, first published in 1941 and issued in editions or reprints five times since its first publication. The literature has also been brought up to date as far as possible. Forty-two illustrations have been added. There is a good index, and the publishing is excellent.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By Frank R. Ford, M.D., associate professor of neurology, Johns Hopkins University School of Medicine. Third edition. 8°, cloth, 1181 pp., with 195 illustrations and 15 tables. Springfield, Illinois: Charles C Thomas, 1952. $18.50.

Dr. Ford has thoroughly revised this new edition of his standard book, first published in 1937. Fifty-three illustrations have been added. Bibliographies have been appended to the various chapters; there is a comprehensive index, and the publishing is excellent. The book is recommended for all medical libraries and to all neurologists.

Physical Diagnosis. By Harry Walker, M.D., professor of clinical medicine, Medical College of Virginia. 8°, cloth, 461 pp., with 126 illustrations. St. Louis: C. V. Mosby Company, 1952. $8.00.

Dr. Walker in this new book has had the assistance of 5 of his associates and Dr. Raymond A. Adams, of the Massachusetts General Hospital. The author has attempted to describe the signs generally considered to be the most valuable. The text is divided into three sections: physical diagnosis, and diseases of the respiratory and circulatory systems. There is an extensive index, and the publishing is excellent.

Progress in Neurology and Psychiatry: An annual review, Volume VII. Edited by E. A. Spiegel, M.D., professor and head of the department of experimental neurology, Temple University School of Medicine. 8°, cloth, 604 pp. New York: Grune and Stratton, 1952. $10.00.

This new volume in a valuable series contains contributions by 75 authors. The material is divided into basic sciences, neurology, neurosurgery and psychiatry. Bibliographies are appended to the various chapters; there is an index, and the book is well published. It is the type of serial that should be in the reference sections of all medical libraries.

A Students' Radiological Mathematics: Elementary mathematics applied to medical radiology. By L. A. W. Kemp, B.Sc., F.Inst.P., physicist to the London Hospital. 8°, cloth, 315 pp., with 128 illustrations. Oxford, England: Blackwell Scientific Publications, 1951. 21 sh.

Dr. Kemp has written primarily for the student. However, his book should prove valuable to radiologists. The text is divided into chapters on algebra, geometry, trigonometry and the handling and presentation of numerical data. Two appendixes give notes on calculus and lists of useful data. The publishing is excellent.

NONCLINICAL NOTES

APPOINTMENT OF DR. WILKINS

Dr. George F. Wilkins, medical director of the New England Telephone and Telegraph Company, was elected president of the Industrial Medical Association at its convention at Los Angeles on April 20-24.

NOTICES

ANNOUNCEMENTS

Dr. John J. Finn, Jr., announces the removal of his office from 270 Commonwealth Avenue, to 5 Bay State Road, Boston.

Dr. Kenneth W. Sinish announces the removal of his office from 8 Porter Street, Melrose, to 60 Summer Street, Lyanfield Centre.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the Prendergast Preventorium of the Boston Tuberculosis Association, 1000 Harvard Street, Mattapan, on Tuesday, June 16, at 12 noon. Dr. Eli Friedman, pediatrician-in-chief, Boston City Hospital, and physician in charge, Prendergast Preventorium, will speak on the subject "Further Observations on B.C.G. as a Tuberculin Test."

Physicians are cordially invited to attend.

(*Notices concluded on page xx*)